Michael J. Keating, MB, BS
February 28, 2012

Slide 1: CLL–Understanding Diagnosis and Treatment

OPERATOR:
Hello, everyone, and welcome to *CLL–Understanding Diagnosis and Treatment*, a free telephone/web education program. It is my pleasure to introduce your moderator Lauren Berger of The Leukemia & Lymphoma Society.

Slide 2: Welcome and Introduction

LAUREN BERGER:
Thank you and hello, everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you. And a special thanks to Dr. Keating for sharing his time and expertise with us today.

We have over 1,800 individuals participating from across the United States and many international participants from Argentina, Australia, Bangladesh, Barbados, Canada, Germany, Guatemala, Israel, Korea, Pakistan, Philippines, Singapore, Spain, Sweden and Uruguay.

We would also like to thank and acknowledge Teva Oncology for their support of this program.

Before we begin, I'd like to introduce The Leukemia & Lymphoma Society's President and CEO John Walter, who will share a few words. John?

JOHN WALTER:
Thank you, Lauren. I'd like to add my welcome to all of you. We are fortunate to have as our presenter today Dr. Michael Keating, one of the nation's leading experts in CLL. We appreciate Dr. Keating's dedication to supporting the mission of The Leukemia & Lymphoma Society through his research and care of patients with blood cancers. I would like to thank him for providing us the latest information on CLL diagnosis and treatment.

The Leukemia & Lymphoma Society is committed to bringing you the most up-to-date information about your blood cancer. We know it is important for you to stay current, so that you can work with your healthcare team to determine the best options for the best outcomes. Our vision is that one day the great majority of people who have been diagnosed with a blood cancer will be cured or will manage their illness with good quality of life.

Since 1954, LLS has awarded more than $814 million to fund research, specifically targeting blood cancers. We will continue to invest in research for cures and programs and services that improve the quality of life for patients and their families. This program is one step on the road of your journey to managing your life with CLL.

Thank you and I'll turn the program back over to Lauren.

Michael J. Keating, MB, BS
February 28, 2012

LAUREN BERGER:
Thanks, John.

I'm now pleased to introduce Dr. Michael Keating, Professor of Medicine and Internist in the Leukemia Department in the Division of Cancer Medicine at the University of Texas MD Anderson Cancer Center in Houston. Dr. Keating, we are so privileged to have you with us today and I'll now turn the program over to you.

Slide 3: CLL Some things you need to know

DR. MICHAEL KEATING:
Thanks very much, Lauren. I'm very privileged to have so many people wanting to hear what we have to say about CLL. And for those of you who don't know, I have effectively become a one trick pony, that the only patients that I ever see these days really are patients with chronic lymphocytic leukemia. And this was thought to be a very boring disease years ago, but it has now become one of the most fascinating areas of research and one in which we're making tremendous progress.

But there are a lot of things that are hard for patients to get their arms around, so I thought that we'd tell you some things that I think you really do need to know as part of your CLL.

Slide 4: Chronic Lymphocytic Leukemia
So in this slide we have some information on CLL. It is the most common adult leukemia and as you'll notice there, the median age or the average age at diagnosis is 72 years, which means as our society gets older there are going to be more and more patients that fit into this category. But unfortunately a lot of the research is not done on the older patients because they tend not to come to referral centers and we're trying to change that attitude so that we can get more user-friendly treatments that will be effective to older people.

As you can see, the number of deaths per year is substantial and we need to get that down quite dramatically, but the survival really has improved quite dramatically over the last few years as I'll demonstrate for you.

Slide 5: Diagnosis: NCI-WG
The diagnosis of CLL ends up being fairly straightforward in most circumstances in that the patient usually comes in presenting with either fatigue or they feel some lumps and bumps and many patients these days are diagnosed on a coincidental blood test. So that to confirm the diagnosis we check on the blood and in some cases it is necessary to check the marrow, but not necessarily for the diagnosis. And when we look at the blood we find by putting the cells through a flow machine, that we can identify that there are different proteins on the surface of the cells and these proteins are immunoglobulins, as you can see there, IgM or IgD. And normally there is a split between the Kappa and Lambda parts of the protein. But in CLL they're all either Kappa or Lambda, so it's a single clone.

And then you look at the proteins on the surface which are characteristic of B lymphocytes because 97, 98 percent of all CLLs involve the B lymphocyte, not the T lymphocytes. And you can see that CD19, 20 and 23 are all keys to the diagnosis. If there's a negative CD23, it suggests that it may be a variant form of CLL and additional testing then needs to be done.

Michael J. Keating, MB, BS
February 28, 2012

DR. MICHAEL KEATING:

And there is a protein which is normally only present on T lymphocytes, called CD5, but it is present in all of the patients that have CLL.

Slide 6: Staging Systems

Now many years ago my friend and colleague Dr. Kanti Rai developed a staging system so that patients that just had an increase in their lymphocytes in the blood were considered Rai stage zero because many of these patients never progressed. But as the lymph nodes became enlarged or the spleen or the patients developed anemia or a low platelet count, known as thrombocytopenia, the Rai stage increased and the survival decreased.

And subsequently Professor Binet in France modified the staging system a little bit, so that the Rai staging system is used in the United States and the Binet system often is used in Europe and other countries.

Slide 7: Traditional Prognostic Factors

So there are a number of prognostic factors and a prognostic factor is something that tells you the likelihood of patients living and the patients likely to have long remissions.

So the traditional ones that have been put in place have the stage of the patients when they come in. If the patients are in the watch and wait category, we try and calculate how rapidly the lymphocyte count is doubling. And it doubles in log fashion or logarithmic fashion, so that it takes the same amount of time to go from 10 to 20, 20 to 40, 40 to 80, etc., rather than just 2 to 4 and 4 to 6 and 6 to 8, etc.

So if a bone marrow is done the only bad characteristic is if the vast majority of the marrow is occupied with CLL cells. And as time goes by we have found out that patients that are older and particularly if they're men, have a shorter survival. And as I'll explain shortly, there is a strong association with chromosome abnormalities or cytogenetic abnormalities.

Slide 8: Newer Prognostic Factors

Now the reason we do this test that's called the FISH test, if we're trying to get some information on the genetics in acute leukemia and some other diseases, the cells divide readily and the chromosomes separate and we can tell if it's a normal number and the normal confirmation of the chromosome changes. But CLL cells tend not to divide, so we have to do what's called FISH or fluorescent in situ hybridization.

Now what that means is that there are probes of DNA that will attach to particular parts of the chromosome and normally there will be two chromosomes of the same number and the same length, so that there will be two fluorescent dots that you see on the slide preparation. But if you lose part of the chromosome or the whole chromosome, it's called a deletion. And if you have an additional chromosome it's called a trisomy. So that as you can see, the abnormalities in CLL involve chromosome 17, 11, 12 and 13. And the more favorable ones are the ones that are abnormalities in 13 and those that have a normal pattern.

Michael J. Keating, MB, BS
February 28, 2012

DR. MICHAEL KEATING:
Every CLL patient has a unique antibody gene or immunoglobulin gene, called the immunoglobulin heavy chain variable region. And in normal B lymphocytes there is a process of mutation that goes on, so that there are parts of the gene which are chopped out and joined up and if there is less than 2 percent mutation it's called unmutated and the mutated patients have a far superior survival than the unmutated.

There are some other additional tests that are done. A protein on the surface of the cell called CD38 and the higher, the less favorable the outcome. And a test which is somewhat complicated to do is the ZAP 70 test, and again it has an adverse outcome. And if there's a high level of beta 2 microglobulin, this also tends to be adverse.

So as you can see, there are a lot of characteristics and no one characteristic is the whole answer. So that it's a complicated issue and I would encourage patients not to worry if they have one or two abnormal tests because all that they tell you is the likelihood of the disease progressing.

Slide 9: Genetic Aberrations in CLL
So the frequency of these abnormal changes is illustrated here. And far and away the most common one is loss of part of chromosome 13 in the q or the long part of the chromosome. The next one is loss of part of chromosome 11. Additional chromosome 12. Loss of part of 17p, which is the short arm of that chromosome. It's only in 7 percent. Which is important because this is the genetic change which is most feared by patients and their physicians because it's more difficult to deal with. And some patients have lost other chromosomes, as you can see, with the 6q.

So this is an important test because it's emerging that this gives a lot of information on the natural behavior of the CLL and the likelihood of responding.

Slide 10: IWCLL Indications for Treatment
Now there's a very complicated indication for treatment, but basically if patients have advanced stage or a very big spleen or very big lymph glands or if under observation the lymphocyte count continues to rise rapidly or if the patients have antibodies that are attacking the red cells or the platelets, and this is autoimmune anemia and thrombocytopenia, or significant symptoms and failure of production of normal blood cells, these are the indications that we have for treatment. And it's not always cut and dried. So don't hold everyone to a fixed form of this because there are a lot of clinical features that measure in.

So if the patient develops anemia and thrombocytopenia, they're Binet stage C and Rai stage 3 and 4. And these patients go on to treatment.

Slide 11: Previously Untreated CLL Treatment Options
Now there has been a very dramatic change over time. In the era of the 60s and the 70s, there were a group of drugs called alkylating agents which bind to DNA and the commonest one, chlorambucil or Leukeran® and cyclophosphamide or Cytoxan®. And then in the 1980s a group of drugs called the purine nucleosides and fludarabine is the most commonly used one. And then this was combined with the alkylating agents in the 1990s. And in the 2000s we then had chemo-immunotherapy, where chemotherapy was combined with antibodies such as rituximab and more recently alemtuzumab or Campath® and bendamustine or Treanda® have been approved for the management of CLL.

Michael J. Keating, MB, BS
February 28, 2012

DR. MICHAEL KEATING:

Slide 12: Defining CR in CLL
Now the goal in management of most leukemias, lymphomas and cancers is to get a complete remission. And to do that we have to get rid of the leukemia and get rid of the patient's symptoms, so that they're free of symptoms, the lymphocyte count becomes normal, you can no longer feel the abnormal lymph glands or liver or spleen, and the normal neutrophil count, platelet count, hemoglobin levels are achieved. And in the bone marrow you have a normal percentage of lymphocytes with no clusters of leukemic cells.

So in the past, up until probably the 1980s when fludarabine came along, only about 5 percent of patients were able to achieve this, but as I'll show in two slides ahead, we actually are doing very much better than that these days.

Slide 13: IWCLL Role of CT Scan
So there's also some discussion at the present time as to whether we need CAT scans. And this has never been part of the evaluation of CLL response or indications for treatment. But it is sometimes useful and it's been recommended that we conduct some research of this in clinical trials. But I would warn you against having multiple CAT scans unless there's a very clear indication for it. It's done very commonly in lymphoma, but a lot less commonly in CLL.

Slide 14: Response to FC + Rituximab
So the standard recommendation for treatment approved by the FDA these days is a combination of fludarabine, cyclophosphamide and rituximab. And this was the data that we achieved on 300 patients treated at MD Anderson. And as you can see, the complete remission rate has now gone up from about 5 percent up above 70 percent in our experience.

Now one of the things you have to be cautious of is that the majority of patients that come to centers such as ours are healthier patients and they tend to be younger and they tend to be more affluent. So that while we're very happy that we've got this response, it doesn't necessarily translate to people that have a lot of illnesses and those that can't conveniently get in for their different treatments.

Slide 15: FCR-300 Survival and Time to Fail
Now this is what we call a survival curve and a time-to-treatment failure curve. And as you can see, on the vertical axis up to 1.0, that's 100 percent of the patients are alive and as time goes by on the yellow curve, the number of patients that are dying continues to increase. But we're now getting to the point where about close to two-thirds of the patients are still alive ten years after starting their treatment. And in the green curve you'll see that about 40 percent of the patients have not had any recurrence of the leukemia at ten years or more.

Now to put that in perspective, before this sort of chemo-immunotherapy came along, we were left with a situation that the average survival was around about five years and the average time-to-treatment failure was about three years. And both of those have effectively doubled with the chemo-immunotherapy era.

Michael J. Keating, MB, BS
February 28, 2012

DR. MICHAEL KEATING:

Slide 16: CLL-8: Study Schema
Now you might say well, that's only one institution, and fortunately our German colleagues decided to do a study where they compared FC, fludarabine and cyclophosphamide, compared to the same two drugs with rituximab. And the complete response rate was double with the addition of rituximab and there was a significant survival advantage and this convinced the FDA that they should lead to the approval of this as treatment for younger patients. And there's still a lot of debate as to what the most effective treatment is for patients over the age of 65 and 70. I still think that in the right circumstance FCR is very good, but there's a lot of research now being conducted with oral medications to try and improve the tolerability of the treatment for patients.

Slide 17: Is FCR good for everyone?
Now the question that comes up, okay, FCR is good, but is it good for everyone? And the answer to that is that it is good, but it's not as good as we would like it to be.

So as I mentioned, the immunoglobulin gene, if it's more like a normal B cell, it's mutated and the mutation status is important. Loss of chromosome number 17 with a mutation in a protein called P53 and 11q with a loss of a gene called ATM. And the older patients, and we have to look at that to see whether they're beneficial or not.

Slide 18: FISH Cytogenetics and Mutation Status
So I'll now address the impact of the FISH genetics and the mutation status on probability of responding to the FCR type regimens.

Slide 19: Prospective Evaluation of Prognostic Factors Post FCR Study
And here you have the value is the different chromosome change. The number of patients is illustrated in the second column. And as you can see, the only chromosome abnormality that has less than 66 percent complete remission rate is the 17p abnormality and all the others have a fairly satisfactory response rate.

Slide 20: Time to Fail Untreated CLL Age <70 by FISH
So to put this another way, if we look at the time to the failure of treatment, the yellow curve shows you that about 50 percent of the patients that have abnormalities in chromosome number 17 have failed their treatment at one year and only a small proportion, about 25 percent, will have long-term control of their disease.

The patients that have lost part of chromosome 11 do fairly well initially, but after that they all appear to fail after about three years. And the rest of the patients in the white curve are doing significantly better.

Slide 21: Mutation status, zap 70 and CD38 are not good predictors of CR!
So the mutation status ZAP 70 and CD38 are not predictors of the probability of complete remission and the only feature that does predict is the 17p abnormality.

Michael J. Keating, MB, BS
February 28, 2012

DR. MICHAEL KEATING:

Slide 22: FCR Time to Progression by Mutation Status
If we look at the importance of the mutation status, however, while it doesn't predict who gets into remission, it does tell you how long they're going to be in remission. And this is a different survival curve because on the vertical axis, going up, is an algorithmic scale. And as you can see in the end of that curve, about 70 percent of the patients that are mutated are expected still to be in remission, no sign of the disease coming back out to ten years. Whereas in the green curve, the unmutated patients all tend to relapse with an average time to relapse of around about five years.

Slide 23: New Treatments for CLL-2012
So we need to do better, particularly for the unmutated group of patients. And fortunately there are a number of new treatments that have come along for CLL. And as you can see, ofatumumab, bendamustine have been approved for the treatment of CLL, usually in previously treated patients, but bendamustine can be used up front. There is also a new group of oral medications called CAL 101 and a BTK inhibitor called PCI32765, that are oral and they block the signaling or activation of the CLL cells.

Now down further you'll see there's a drug called lenalidomide or Revlimid®, which I'll discuss, because it's emerging as a very significant new drug in the management of patients with CLL. And a number of you will have heard about the chimeric androgen receptors or the CARs that were studied up in University of Pennsylvania by Dr. June and his colleagues and this is going to emerge as a very important element. And allogeneic transplants are also a very important component.

Slide 24: Bendamustine
Now the chemotherapy drug which has been recently approved is bendamustine, which has in its structure an alkylating agent group and a purine-like group, so one is like cyclophosphamide and the other is like fludarabine. And it was used a lot in East Germany for a long period of time and now it's got into the rest of Germany and the Western world. And it's been very favorably looked at by the FDA and we have now got to the point where this is approved and is being combined with rituximab in a number of different areas.

Slide 25: Refractory CLL
Alemtuzumab has been approved for patients that have had prior therapy and are refractory to it. It's a somewhat difficult drug to use unless patients and their doctors are well informed, because it tends to be associated with a number of attacks of shivers and shakes during the first week of infusion and that gets better. But reactivation of different viruses can occur and a number of people will get a variety of infections. So this is a drug which has to be used wisely and skillfully and appears to be quite effective in patients that have chromosome 17 abnormality.

Slide 26: Tumor Flare Reaction
Now one of the agents which is very important, however, is lenalidomide. And unfortunately when we give this to patients initially, some patients will develop a flaring of the lymph glands. And as you can see in the picture, there is a red swollen area, which then after a week or so will subside.

DR. MICHAEL KEATING:
And we can prevent that from occurring in a number of ways. We can give nonsteroidal anti-inflammatories like Aleve®, etc. And they will control the symptoms quite well. But some patients will require steroids to be given.

Slide 27: Prevention of Tumor Lysis Syndrome
Now the other thing is that sometimes lenalidomide or Revlimid, when it's given, will be associated with rapid dissolving of the cells. And so for the first week you have to check on this very closely by giving patients a lot of fluid and making sure that their kidneys are functioning quite well.

Slide 28: Lenalidomide in Elderly CLL
Now that being said, there have been some studies that have been undertaken, looking at lenalidomide in patients over the age of 65, and while there's a relatively low complete response rate, the overall response rate in patients over the age of 65 is 62 percent.

Slide 29: Lenalidomide in Elderly CLL
One of the pleasing features is when we looked at what happened to the gammoglobulin levels, there are two important immunoglobulins or antibodies, the IgM and the IgG, and this is the only drug that we know which increases the levels of these normal proteins and help the patients resist infection.

Slide 30: Lenalidomide in Elderly CLL
And if we look at the longer term outcome, in the green curve you'll find about a third of the patients will fail the treatment in the first year, but after that they go along for a very long period of time and at last fall off, in the green curve, is just a statistical anomaly. The longest follow-up patient relapsed at that time.

Now the favorable feature, however, is if we look at the survival curve, more than 80 percent of the patients are alive at four years, which is very encouraging for the older group of patients. And many of these patients are very stable, taking one pill a day for four years or more.

Slide 31: New Antibodies
Now when we talk about the antibodies, the most commonly used one is an antibody called Rituxan or rituximab. But there are some new antibodies that have come along and the one which has been approved for patients that have had a lot of treatment before is a drug called ofatumumab or Arzerra®.

Slide 32: Ofatumumab: Characteristics
And the rituximab and ofatumumab both bind to this protein called CD20, but they bind at different parts of the molecule.

Slide 33: Ofatumumab in Refractory CLL
And if you look at the overall outcome with ofatumumab or Arzerra in patients that have had a lot of treatment before, the patients in the orange are patients that have failed fludarabine and failed Campath or alemtuzumab, and half of these patients will respond, whereas it was only expected that about 15 percent of

Michael J. Keating, MB, BS
February 28, 2012

DR. MICHAEL KEATING:
the patients would respond. And in the patients that have very bulky disease, with refractoriness to fludarabine, almost a half of those patients responded. So this is a new powerful CLL drug and getting increasing usage as more clinical trials are brought into place.

Slide 34: B Cell Receptor Signaling
Now there's a B cell receptor on the surface of the cell, which I'll show you in this next slide.

Slide 35: B Cell Receptor Signaling Pathway
And on the surface there's this green part of the molecule, which is the B cell receptor, and normally in a B lymphocyte, a virus, for example, the hepatitis virus might come and attach to this B cell receptor, and stimulate a pathway going down through a thing called LYN and SYK and the PI3 kinase, PI3K, and Bruton's tyrosine kinase or BTK. And that sends signals to the nucleus that makes the cells proliferate.

Slide 36: CAL-101
And there have been, fortunately, a number of drugs that have been coming along that inhibit PI3K and BTK, and one of them is a drug called CAL 101 and this is the structure. It's given by mouth, it's very well absorbed, and it's given by a pill twice a day. And it's been very, very successful in shrinking lymph glands down.

Slide 37: PCI-32765
The other is a drug called PCI32765. A similar small molecule given by mouth once a day.

Slide 38: ALC versus LN Response: Continuous Dosing
And this next slide is somewhat complicated to look at, but if you look at the black box up in the top right hand corner, those big chunky things on the front and to the right are big lymph glands. And as you can see, after two months on treatment these big lymph glands have disappeared. But at the same time the white cell count, the lymphocyte count, has gone from 20,000 at the start, getting up to around about 60,000 and not going down for a period of about three months.

Now what's the outcome of all this? Well, these drugs are in very active research at the present time and they appear to work on the vast majority of patients with CLL.

Slide 39: CLL 5 year + 10 year Time to Fail by Decade
So are things getting better? And this is illustrated in the survival curves of the time-to-treatment failure of patients going on treatment and different decades. And the yellow is the era of the 70s, the green in the 80s, the white in the 90s, and in the new millennium the blue curve shows that there is a very dramatic improvement in the five and ten year failure for relapse of patients going on to clinical studies.

Slide 40: Frontline Treatment of CLL 2015
So that I'm anticipating in the future that we will be treating patients with one of these oral medications that's not a chemotherapy drug. It will be given once a day, probably with monoclonal antibodies.

Michael J. Keating, MB, BS
February 28, 2012

DR. MICHAEL KEATING:
We will then be measuring whether there are remaining leukemic cells by some more sophisticated techniques. We'll be able to decide whether to use the patient's own cells or chimeric androgen receptor cells to kill off the leukemic cells and reserve the stem cell transplants from a brother, sister or an unrelated donor until later on in the course of the disease.

Slide 41: Other Issues Remaining in CLL
There are some other problems that we have to deal with. One is that autoimmune complications when the patients will develop proteins or antibodies which attack their red cells and platelets is important. About 5 to 7 percent of patients going on to treatment will eventually develop a transformation into a large cell lymphoma, which is a somewhat scary circumstance at the present time. The patient's gammoglobulin or antibody levels, the normal antibody levels go down, there is an increase in second cancers that occur, particularly skin cancers and melanoma. There is a tendency to develop infections over time. And eventually if the disease keeps coming back, bone marrow failure can occur. And all of these issues are under very active investigation at the present time.

So I think it might be time now, you've patiently listened to me for about 25 to 30 minutes, for us to answer some of the questions which are most important to you. So I'd be quite happy to entertain the questions that are forwarded to me. Thank you very much for listening.

Slide 42: Question and Answer Session

LAUREN BERGER:
Thank you so much, Dr. Keating, for your very clear and informative presentation. And as you just indicated, it's time for the question and answer portion.

So the first question is from Harriet, it's from the web, and she asks, "How routinely are all these diagnostic tests done for CLL patients and are they just happening at research institutions or do you find that many community oncologists are also doing these?"

DR. MICHAEL KEATING:
The answer to that is that the FISH test has become fairly commonplace now. Because we're a lot more familiar with thinking of chromosome changes and the genetics of all cancers is becoming more commonly investigated, not only in leukemias and lymphomas, but also in solid tumors. However, the mutation status is not done routinely and it is a very, very useful test because it predicts the patients that are going to remain without treatment for a long period of time, and it also gives you the best expectation of long-term outcome. So that the message that we're giving to doctors out in the community is do the FISH test before you make a treatment decision and then if you want to figure out how long the patients are going to be in remission, do the immunoglobulin mutation status.

One of the tests that we didn't talk about very much is the Beta 2 microglobulin test, which is a simple inexpensive protein test in the blood, which gives us a lot of additional information on likelihood of response.

Michael J. Keating, MB, BS
February 28, 2012

LAUREN BERGER:
Thank you. We'll take the next question from the telephone audience, please.

OPERATOR:
Our next question comes from Patrick in Tennessee.

PATRICK:
Dr. Keating, I would like to have you expound on in your practice, the appropriate use of stem cell transplant, when you think it's appropriate and when you don't. Thank you.

DR. MICHAEL KEATING:
This is probably the most difficult decision that a physician and patient have to make together. Because many patients were told initially when they came in that they'll probably die of something other than CLL. And then after a period of time when their disease doesn't respond very well to treatment or if the 17p abnormality is noted in their leukemic cells, or if other complications occur, the doctor suddenly – hopefully not suddenly – but starts to discuss the possibility of a stem cell transplant.

The recommendation at the present time is that if you have a patient that has an abnormality in chromosome number 17, that after initial attempt at therapy to reduce the amount of leukemia, the patients would then get a stem cell transplant from a brother, sister or an unrelated donor, while they're in remission or close to a remission.

However, if the patients respond to their first treatment, then relapse and then don't get a very good response to their first what they call salvage therapy, this is again another indication that a stem cell transplant is appropriate.

Now the rest of it gets to be very fuzzy because there's a lot of individuation at that point. I will tell you at the present time that the non-ablative stem cell transplants or the mini-transplants have enabled us to go from offering transplants only to patients under the age of 50 or 55, up to patients in the 70 to 75 year age range. And up until recently it was the only potentially curative treatment.

So there's no simple answer to it. It ends up being a dialogue between the doctor and the patient. And actually there's a dialogue between the chemotherapy hematology type doctors and the stem cell transplant doctors, to choose the best time and the greatest probability of response. And I would recommend that if you do have the opportunity to go to one of the major centers that does a lot of transplants in CLL, not just transplants generally, and these tend to be the Fred Hutchinson Cancer Center, the Dana-Farber Cancer Institute, the MD Anderson Cancer Center, Ohio State and UC San Diego, tend to have a lot of transplants specifically for CLL.

LAUREN BERGER:
Thank you for your question, Patrick. And we'll take the next question from the web and Barbara asks, "What are the side effects of long-term maintenance using Rituxan only?"

Michael J. Keating, MB, BS
February 28, 2012

DR. MICHAEL KEATING:
Well, the main thing that happens with Rituxan as a single agent in CLL is that you can develop a lowering of the gammoglobulin levels, the normal antibodies, because rituximab attacks the leukemic cells, but it also attacks the normal B lymphocytes. So this is the major complication that occurs. A small number of patients will develop rashes and joint discomfort or low neutrophil count, but the thing is that it's not a very good long-term control agent. It tends to cause responses in about two-thirds of patients as their first-line treatment, but the responses usually only last 15 to 18 months and very few people are in long-term control.

LAUREN BERGER:
Thank you. wW'll take the next question from the telephone audience, please.

OPERATOR:
The next question comes from Richard in Illinois.

RICHARD:
Doctor, thank you so much. I received 100 percent disability because I got chronic lymphatic leukemia at 57. All the Navy people get it at 57. And could you talk about that?

DR. MICHAEL KEATING:
Well, there's relatively little information that's available to us as to why the military has chosen to do this approach to CLL. And so that there is some information, but it's not published as to what the outcome is and whether different agents or different occupations in the military have been associated with causing CLL or aggravating CLL. So one of the difficulties that we have is that we don't have ready access to the data, so that we can't really give you very much wise counsel in that area.

LAUREN BERGER:
Thank you for your question, Richard. We'll take the next question from the web and this question is from Ronald and he asks, "After relapse why is it preferred to wait for more symptoms before treatment? Isn't it more difficult for the patient to withstand side effects?"

DR. MICHAEL KEATING:
Yes, I think that to clarify what happens, when patients are first diagnosed, if there's not a clear indication for treatment, the patients are observed for a period of time to see if the disease is progressing. And a certain number of patients, particularly if they're diagnosed early, will go for years without needing treatment and some patients never need treatment and will have a stable form of CLL up to 10, 15, 20, 30 years. So that the watch and wait strategy is to try and identify those patients.

Now once the patient has progressed, and needs to go on to treatment, if they recur, I don't think the watch and wait is necessarily a good strategy. But there are sometimes, if the patient has early relapse and there's no symptoms, you'll get some idea of how aggressive the relapse is by observing them for a period of time.

DR. MICHAEL KEATING:
But as soon as it becomes clear that the relapse is progressing, that's the time that you should consider initiating therapy. You should not wait until the patients have developed bone marrow failure or until they get significant symptoms, in my opinion, because they've already demonstrated that they have progression of their CLL.

LAUREN BERGER:
Thank you for your question, Ronald. We'll take the next question from the telephone audience, please.

OPERATOR:
The next question comes from Joanne in Rhode Island.

JOANNE:
Yes, Doctor, my daughter has multiple myeloma and my father-in-law had CLL. I was wondering what kind of a link it is between the two of them. Because it's a B cell?

DR. MICHAEL KEATING:
There's not a strong link, but there is an association of CLL with other B cell diseases. More commonly in lymphoma than it is in multiple myeloma. There is a familiar nature of CLL, so that if a patient has CLL and it just occurs out of the blue, without any past family history, the likelihood of people, of their brothers, sisters and children having CLL, is about four times more likely than the average population.

But four times rare is still rare. So I would encourage patients not to worry too much about their brothers and sisters and children. It's only really where you have multiple people in the genetic tree that are involved that it becomes truly a familial CLL and that is an area that's under very active investigation at the present time. Because there may be some genes that are involved, but so far we haven't been able to clarify any dominant gene that's associated. So myeloma, a soft association, not a very strong one.

LAUREN BERGER:
Thank you for your question. We'll take the next question from the web audience and Donna asks, "Is treatment an option for patients with other health issues such as heart problems or diabetes?"

DR. MICHAEL KEATING:
Well, in the past we used to worry mainly about getting rid of the leukemic cells and the treatment which was given in those days was a simple oral medication called chlorambucil or Leukeran, which was not terribly effective, but it was easy for the patient to take. But in all illnesses if the patient has other diseases or comorbidities, there is a greater likelihood of having complications occur.

There is a lot of research that's now being done to develop what they call comorbidity scores and the first one is a thing called the CIRS or the CIRS Score. And this has been popularized by the Germans and the more illnesses that you have, such as if you have emphysema or if you have cirrhosis of the liver or kidney disease, etc., these are all considered substantial comorbidities and it increases the risk of treatment.

Michael J. Keating, MB, BS
February 28, 2012

DR. MICHAEL KEATING:
The Germans have popularized a thing called the go-go status for the patients that are young and don't have other illnesses. There is a slow-go treatment for patients that are over the age of 65 or 70 or have illnesses. And patients that are older and have a lot of comorbidities are considered no-go's.

But I will tell you that with these new medications that inhibit the B cell receptors such as CAL 101 and the PCI32765, that these medications are very well tolerated and we've treated a number of patients with very significant comorbidities that have had very dramatic responses.

So I think that it does create a challenge for us and we can't give you very clear ideas of the increased risk according to whether it's diabetes or whether it's cardiac problems. I worry a little more if the patients have a history of chronic lung disease because the infections that tend to occur in CLL tend to be sinus and pulmonary infections.

LAUREN BERGER:
Thank you for your question, Donna. We'll take the next question from the telephone audience, please.

OPERATOR:
The next question comes from Trudie in Florida.

TRUDIE:
Dr. Keating, I was diagnosed with angioedema, ulcerative colitis prior to my CLL diagnosis. One of my doctors had suggested, he thought the three were connected, meaning they were all autoimmune. My son also has Crohn's disease. Could that be because I have CLL?

DR. MICHAEL KEATING:
Well, I can tell you that before CLL is even diagnosed, we have some mouse models now that you can cause CLL to occur in mice, in about 40 percent of the mice that have some genetic manipulation. And before they develop the CLL, you can find that their immune system is very abnormal. It's a very complicated situation. The only common autoimmune complications that occur, antibodies against the red cells and the platelets and to a lesser degree other blood cells. So that the autoimmunity tends predominantly be associated with blood cells, rather than other autoimmune conditions. There's not a high incidence of rheumatoid arthritis or lupus. There are some patients that do develop immune kidney disease, but they're very uncommon. So that while we're always suspicious when there are clusters of autoimmune diseases in a family, that there is some link, we haven't been able to provide that link.

LAUREN BERGER:
Thank you for your question, Trudie. We'll take the next question from the web audience and Carol asks, "How often should you have FISH done? I have 17p and 13q and high ZAP greater than 70. No treatment ever. And it's coming up to 15 years with CLL. I am now 54 years old."

Michael J. Keating, MB, BS
February 28, 2012

DR. MICHAEL KEATING:
Okay, well, the first thing I would say is congratulations. I cheer every time I hear these things happening. Now that we know that patients that have early stage disease and don't have any symptoms, even if they have the chromosome 17 abnormality, a certain number, and it's usually women that don't have progression of their disease for a long period of time. So that's a very good bit of news.

The only time that I would repeat the FISH is if there's a change in the clinical condition. So if the disease begins to progress, I would then consider repeating the FISH. If you're lucky enough to go into a spontaneous remission, I would then do it just for interest to see if the chromosome abnormality has disappeared. I have three patients that I follow that are all women with a low level of 17p abnormality, that the chromosome abnormality appears to have disappeared.

LAUREN BERGER:
Thank you, Carol. And we'll take the next question from the telephone audience, please.

OPERATOR:
Our next question comes from Alan in Wisconsin.

ALAN:
How long is it possible to go without getting treatment?

DR. MICHAEL KEATING:
The longest patient that I have followed has been going out for more than 30 years without needing treatment. I will tell you another thing, because so many patients are having blood tests done these days, there will often be a slight increase in the percentage of lymphocytes on blood tests that are done for other conditions. When we then go and test these lymphocytes we find that they resemble CLL cells, but they're usually less than 5,000 in number, and these patients will have not the disease CLL, but what we call a monoclonal B cell lymphocytosis. That is that they have a clone of cells and they have too many of these cells, but they're all identical, but they don't progress. And this condition of MBL or monoclonal B cell lymphocytosis is associated with progression of the disease to treatment at the rate of about 1 percent per year. Patients that would never have been diagnosed in the past because we didn't have the sophisticated flow cytometry machines to identify that these cells were a discreet family of cells. So this is something that we need to be informed about. If you are diagnosed to have CLL with a very low lymphocyte count, you should ask the doctor if you have MBL. Because it's important, if people are trying to get insurance coverage and various other activities, so that it's important that we have the opportunity to explain to people that just having too many lymphocytes doesn't mean that the patient's at risk, and the majority of these patients live a normal life expectancy.

LAUREN BERGER:
Thank you for that question, Alan. We'll take the next question from the web and Carl said, "I have LGL. Are there any common CLL treatments that would be of interest to an LGL or a LGL leukemia patient, large granular lymphocytic leukemia?"

Michael J. Keating, MB, BS
February 28, 2012

DR. MICHAEL KEATING:
No, it's a very uncommon condition and oftentimes patients don't need any treatment at all. Sometimes it's associated with enlargement of the spleen and there will be suppression of the normal blood counts and occasionally a splenectomy needs to be done. A number of patients have been treated with drugs that suppress the immune system, such as a drug called cyclosporine. Others are treated with methotrexate. But it's such an uncommon condition and so diverse in its characteristics that there's not a clear pattern of successful treatment that we've identified. I think we'll eventually develop a way to identify that these patients have different mutations in their genes and at that time very specific treatment will be undertaken. But most of these patients can live very long periods of time in good health without needing anything to be done. And occasionally they'll need hormones to stimulate their red cells and platelets and their neutrophil count.

LAUREN BERGER:
Thank you for that question. We'll take the next question from the telephone audience.

OPERATOR:
The next question comes from Dave in Wisconsin.

DAVE:
Whenever a person is treated for CLL, the risk of other things increases, such as kidney problems and liver problems and secondary cancers. I was just wondering statistically which of these are the most likely. And if you're talking just about cancers, what are the cancers that are secondary cancers that are statistically the most likely?

DR. MICHAEL KEATING:
Liver and kidney issues are not common as complications. The most common second cancers are the Richter's transformations, when you develop a large cell lymphoma in association with the CLL. And they sometimes come from different families of cells. The other is there's about a 5 percent likelihood of patients developing either an acute leukemia or something called a myelodysplastic syndrome, so that the incidence of this is about 5 percent of patients going on treatment. It's predominantly in older patients and predominantly in men rather than women. Melanoma is about 4 to 6 times more likely to occur in CLL patients than patients of the same age and sex. And a number of patients will develop repeated basal cell cancers, which are a form of skin cancer, and squamous cell cancers. But the most common malignancies, namely breast and lung and colon, are only marginally increased in frequency. So that I'd recommend all CLL patients have a regular relationship with a dermatologist. There are a lot of men that have prostate cancer, but prostate cancer is very common in men of CLL age anyway and there doesn't seem to be a striking increase in the risk.

Lauren Berger:
Thank you for that question and we'll take a question from the web. Richard asks, "How do you see gene therapy coming into play with regards to CLL treatment in the future?"

Michael J. Keating, MB, BS
February 28, 2012

DR. MICHAEL KEATING:
I think the major problem that we have in gene therapy is to identify the dominant gene because we're now getting the situation where if we do a lot of fancy next generation sequencing or deep sequencing, we're finding five, ten, twenty different abnormalities and the question is which one is the dominant characteristic. So that until we find a single gene that we can attack, it's going to be very difficult. One of the genes we're very excited about at the present time is a gene called ROR1, which is normally present in all cells at the time of birth and then gets switched off from the cells. But it doesn't get switched off in CLL.

So I think the gene therapy, will be able to develop ways of educating the patient's immune cells to specifically attack the CLL cells through this ROR1 pathway. So that I think it's going to be the element that leads to the cure of the majority of patients with CLL and there are going to be studies that will be very active within the next two to three years.

Slide 43: LLS Resources

LAUREN BERGER:
Thank you for your question, Richard, and thank you for that very interesting answer. It really leads us toward looking to the future.

Thank you for all your questions. Our program has come to a close. Thank you, Dr. Keating, and thanks to all of you. We are so grateful that you have donated your time today and that all of you have listened and asked so many good questions.

We hope many of your questions were answered and this information will help you and your family in your next steps. If we were not able to get to your questions or if we can provide you with additional information and support, please call an LLS Information Specialist toll-free at 1-800-955-4572. You can also reach us by email at infocenter@lls.org.

On behalf of The Leukemia & Lymphoma Society, Dr. Keating and I would like to thank all of you for sharing your time with us today. Good-bye and we wish you well.