Advances in Blood Cancers: Update on Treatment for NHL and CLL

LEUKEMIA & LYMPHOMA SOCIETY®
fighting blood cancers

Lauren Berger:
Hello, I'm Lauren Berger and I'm the Senior Director of Patient Services Programs at The Leukemia & Lymphoma Society.

I'm pleased to welcome Dr. Rebecca Elstrom. Dr. Elstrom is an Assistant Professor in the Division of Hematology/Oncology Department of Internal Medicine at Weill Medical College of Cornell University and Assistant Attending Physician at New York Presbyterian Hospital in the New York.

Dr. Elstrom, thank you so much for joining us today. Can you give us a glimpse of how things have changed since you began treating patients with non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL)?

Dr. Rebecca Elstrom:
Yes, there have really been dramatic changes in the management of non-Hodgkin lymphoma and chronic lymphocytic leukemia over the past ten to fifteen years. Much of this is based on our ever-growing understanding of the biology of cancer cells. I think the single largest change in treatment has been the development of monoclonal antibodies.

As many people know, rituximab or Rituxan® has really dramatically changed the way patients with B cell lymphomas are treated. Rituximab has been shown to improve survival for patients with just about any subtype of B cell lymphoma in which it's been studied. Rituximab is also used in the treatment of CLL. Chronic lymphocytic leukemia is classified as a leukemia, but it's a cancer of B lymphocytes just like NHL.

I think it's important to clarify from the very beginning that there are many different kinds of NHL. Both CLL and NHL are classified as mature B cell malignancies by the World Health Organization.

NHL can arise from any of the subtypes of normal lymphocytes, B cells, T cells or NK cells. But most arise from B cells and that's mostly what I'm going to be talking about today.

There have been multiple classification schemes throughout the years. Each of these take into account an improving biological understanding of how lymphomas develop. We have a better definition of the origin of the cancer cells as well as the changes that have occurred within the cells in order to become cancer.

We think about NHL in terms of indolent lymphomas such as follicular lymphoma, aggressive lymphomas such as diffuse large B cell lymphoma, and highly aggressive lymphomas such as Burkitt lymphoma.

The specific subtype of NHL really affects our approach to treatment and the goals of treatment, so it's very important to understand what kind of lymphoma we're talking about.

Lauren Berger:
Why is it so important for patients to get an accurate diagnosis of their blood cancer subtype?

Dr. Rebecca Elstrom:
It's so important to get an accurate diagnosis because the approach to the patient is extremely variable, depending on the subtype of NHL.

Each subtype has different characteristics in terms of patient symptoms, the genetic or molecular changes within the cancer cell, and the approach to treatment.

A really critical aspect of understanding the subtype of NHL is to understand what are the goals of treatment. For aggressive types of NHL, our goal is to cure the patient, so we approach treatment very aggressively. On the other hand for indolent NHL subtypes and CLL, at this point in time, although we hope it will change, we don't have curative treatment. And therefore our goal is to manage the diseases as chronic diseases, to keep people feeling well, functional and to maintain good quality of life.

There are individual variations within each subtype of NHL and the approach to treatment may also be quite different, depending on the specifics of a patient's disease or the specifics of the patient themself.

Lauren Berger:
Would you please describe how you determine the diagnosis and characteristics of a patient's disease?

Dr. Rebecca Elstrom:
Yes, there have been major advances in diagnostic tests over the past several years. We have better understanding of genetic and molecular findings that help us to determine diagnosis and other findings that can help us to determine outcome for a patient. There's ongoing research to try to help us develop a better understanding of how to use these characteristics to improve treatment for individual patients.

For example, in CLL there are a variety of molecular changes that help to determine prognosis, though at this point they haven't yet impacted on standard of care.

There's ongoing research at this point to try to help advance our understanding of how to incorporate into improving care. An example of this is the 17p deletion in CLL. In general patients with a 17p deletion don't respond quite as well to standard therapy with fludarabine, but we may be able to optimize treatment for these patients by incorporating treatment with alemtuzumab or Campath®.

Stem cell transplantation may also be considered for these patients earlier than it may be for other patients.

In addition, in diffuse large B cell lymphoma we're learning about new biomarkers. For example, over-expression of c-Myc in diffuse large B cell lymphoma may be an important aspect to recognize and that it may be helpful to change our therapy from the standard at this point of R-CHOP.

In addition, there's a better understanding of different kinds of diffuse large B cell lymphoma and we're starting to be able to subclassify diffuse large B cell lymphoma based on the cell of origin or the specific kind of lymphocyte from which it's arising.

Lauren Berger:
Dr. Elstrom, what do you discuss with a new NHL or CLL patient?

Dr. Rebecca Elstrom:
I think one of the first things to discuss is making sure that we have the right diagnosis and to discuss with a patient how that specific diagnosis relates to their treatment options.

An important aspect of discussing management is to define and differentiate grade from stage. Grade means how aggressive the lymphoma is and this is mostly defined by what the lymphoma looks like under the microscope. For example, follicular lymphoma, although we tend to think of it as a low grade lymphoma, has three different grades and these are very precisely defined grades, based on how many large cells versus small cells the pathologist sees under the microscope.

Grade also refers to the indolent versus aggressive versus highly aggressive lymphomas, as we discussed previously. Grade is really an imprecise measure of aggressiveness of the lymphoma.

Stage, on the other hand, refers to where in the body the lymphoma has spread. It's important to note here that stage has very different implications in NHL when we compare it to other types of cancer.

For example, in aggressive subtypes of lymphoma, the lymphoma is curable, even if it's at stage IV. Whereas for indolent subtypes of NHL, these can be manageable even if they're at stage IV.

In addition, there are good treatments for patients with CLL, even at all stages of the disease.

Another critical aspect of the discussion is to define the goals of therapy. As we've discussed, some types of lymphoma are curable and others we depend on long term management. And it's very important to be clear on what our goal is in treatment.

The goal of treatment really impacts on how we plan the treatment. For example, if cure is the goal, we're going to try very hard to stick to therapy on time and at the appropriate doses. Whereas if cure is not the goal, we may have different characteristics to incorporate.

We also want to talk about treatment options. There are some subtypes of NHL that have a specific standard of care and there are others that have multiple options, such as follicular lymphoma or CLL.

We want to talk about clinical trials because clinical trials may be relevant to any patient that is talking about treatment for lymphoma.

We also want to look forward a little bit to what happens if the patient needs to have treatment again, so that the patient knows that there are possibilities for treatment down the road, even after this initial one.

And I always want to emphasize that clinical trials are always on the agenda, whatever stage of treatment and whatever subtype of lymphoma the patient has.

Let's acknowledge that patients aren't treated by one person alone. The treatment team includes oncologists, nurses and administrative support staff, all of whom are critical to the care of a patient. The team may also expand beyond one office. Many patients are treated by community oncologists and standard therapy can certainly be effectively administered in the community setting. However, it may be appropriate with such rapidly evolving diseases as NHL and CLL, to consult with a blood cancer specialist to ensure the incorporation of the latest information. Again, though, often the actual therapy can be given by community oncologists.

In addition, consultation with a specialized hematopathologist can be very helpful to ensure that the diagnosis is correct and that any subtleties of new biomarkers that may have been identified have been incorporated into the details of the diagnosis.

Lauren Berger:
Dr. Elstrom, how is response to treatment measured?

Dr. Rebecca Elstrom:
The major way that we measure response to treatment in NHL is with imaging tests. The most common of these are CT scans and PET-CT scans. We also measure response in a more informal way, though, through physical exam and discussion of symptoms. If a patient is starting to feel better, their fevers go away, their fatigue gets better, we have a pretty good idea that they're starting to respond.

In CLL, on the other hand, we measure response mostly based on blood tests and bone marrow biopsy, but sometimes a CT scan is relevant in CLL as well.

Lauren Berger:
What questions should a patient ask members of their treatment team to help them get the best result at any phase of treatment?

Dr. Rebecca Elstrom:
Patients should ask whatever questions they need to to be sure that they understand their disease and what the approach to treatment will be. As we've talked about, it's so important to understand the disease subtype in order to understand what's going to happen down the road. A patient should be sure that they understand the goal of treatment, that is can the disease be cured or will the goal of treatment be to manage the disease over the long term. What are the symptoms of the disease? What will be the logistics of treatment? For example, how frequently will the patient need to come in? How long will they need to be here? Will the treatment be outpatient or inpatient?

Patients should be sure that they understand what the side effects of treatment might be. They should understand what medicines will be used to help manage their symptoms.

Another question to ask is what should the patient do if they have symptoms when they're at home, who should they call. And very importantly, are there any specific symptoms that the patient should treat as an emergency.

Another thing to ask about is how response to treatment is going to be evaluated. And along the way, to ask the doctor is this what's expected in terms of response, is the treatment working.

And it's really important to emphasize that it's never wrong to ask for a second opinion. It's fine and it's important for a patient to ask for a second opinion on the diagnosis, that is the pathology, and it's also fine to ask for a second opinion on treatment.

A patient should be sure that they ask about whether there are any clinical trials that might be available for their disease and for their stage of disease.

Lauren Berger:
What are the standard therapies for patients who have NHL or CLL and when do you recommend treatment in a clinical trial?

Dr. Rebecca Elstrom:
It's important to know that there are different standards of care for different NHL subtypes and there are some subtypes that don't have a standard of care. In addition, there may be different treatment recommendations for CLL patients based on their specific disease characteristics.

An example where there is a standard of care is diffuse large B cell lymphoma. R-CHOP chemotherapy is considered the standard and is appropriate for most patients. However, some patients, particularly higher risk patients, may want to seek alternatives or even a second opinion regarding options.

An example where there's not a standard of care is CLL. There are multiple choices for treatment. FCR or fludarabine, Cytoxan® and rituximab, is a common choice, but for some patients other choices may be better.

Another example where there's not a standard of care is follicular lymphoma. Common chemotherapy choices for initial therapy of follicular lymphoma include R-CVP, R-CHOP or R-bendamustine. However, there are also different options other than chemotherapy and for some patients watch and wait may be an appropriate choice.

Clinical trials are appropriate to consider at any point in treatment, especially when there's no standard of care. And they're available for every disease stage.

There are many promising therapies that are being studied in both NHL and CLL.

I'd like to go back for a minute to the concept of watch and wait. This refers to observation of patients who present with indolent lymphomas or CLL, who have no symptoms and have no suggestion of rapid progression of disease. This is a very common approach because at this point in time it has not been shown that early treatment is beneficial in patients who have no symptoms.

There are, however, ongoing studies to see whether there may be some advantages to giving specific treatments at the time of diagnosis of indolent non-Hodgkin lymphoma or CLL, even in patients who would otherwise be observed. The data regarding these aren't in yet.

Lauren Berger:
Dr. Elstrom, would you talk about the role of maintenance therapy, please?

Dr. Rebecca Elstrom:
Maintenance therapy refers to further treatment after an initial induction treatment and it's mostly used in follicular lymphoma and other indolent lymphomas. The agent that's most commonly used for maintenance is rituximab.

In follicular lymphoma and some indolent non-Hodgkin lymphoma, the use of rituximab at scheduled intervals following induction therapy has been shown to prolong the time to progression. However, it hasn't at this point in time been shown to affect what we care most about, which is overall survival.

For aggressive lymphoma subtypes, however, rituximab maintenance has not been found to be helpful.

There are other maintenance therapies that are being studied at this point in clinical trials for NHL, but they are investigational. In addition, in CLL, lenalidomide is being studied in clinical trials of maintenance therapy to see if it may improve long term outcome for these patients.

Lauren Berger:
When should an NHL or CLL patient consider stem cell transplantation?

Dr. Rebecca Elstrom:
There are two major types of stem cell transplantation that may be used in NHL or CLL. Autologous stem cell transplant refers to the transplant of one's own cells and it's really a way to give higher doses of chemotherapy. Autologous stem cell transplant is a standard approach in patients with aggressive NHL subtypes, particularly diffuse large B cell lymphoma that isn't cured by initial treatment. There are other situations where autologous transplant may be considered. In low grade non-Hodgkin lymphoma, for example, follicular lymphoma, it may be considered particularly if a patient has had a short initial remission.

Allogeneic transplant, on the other hand, refers to a transplant from a donor, from somebody else, whose cells are a match to the patient's cells. Allogeneic transplant offers the benefit of a new immune system that may be more effective at fighting the tumor. However, with allogeneic transplant, there's also a higher risk of serious complications or even death from the procedure.

There is an increasing role for reduced intensity allogeneic stem cell transplants that try to decrease the toxicity of the initial therapy that's given before the donor cells. Allogeneic transplant may be considered in some situations for patients with NHL that really hasn't responded well to other therapies, but it's not really a standard approach in most situations at this time.

Lauren Berger:
What role does age play in the treatment of these diseases?

Dr. Rebecca Elstrom:
NHL and CLL are more common in older people and age may be a factor both in choice of therapy and in outcomes of therapy. Regarding choice of therapy, surprisingly age may not be such a significant factor in some specific situations. For example, R-CHOP chemotherapy, the standard for diffuse large B cell lymphoma, can be given to people into their seventies and eighties. And it may be very important to maintain standard therapy in order to optimize the chance for cure.

For patients with coexisting medical problems, however, it may be necessary to decrease the doses of the standard therapy or to consider alternatives.

Even more aggressive therapy, such as stem cell transplant, can be considered for otherwise healthy older patients.

Age becomes more significant if the goal of treatment is not cure, but rather management of the disease. In this setting, consideration of risk-benefit ratios is very important in decision-making. We may want to consider gentler therapies more consistent with maintaining an active lifestyle for many patients with indolent lymphomas.

Regarding prognosis, it's clear that age does affect prognosis. Older patients are less likely to be cured of NHL. Whether this is due to age or due to other factors that are associated with age is still unclear.

The main thing I want to emphasize here is that older patients can be treated for NHL or CLL and treatment decisions are rarely made based on age alone.

Lauren Berger:
What are some of the emerging therapies being studied for NHL and CLL?

Dr. Rebecca Elstrom:
There are a host of exciting emerging therapies and every year there are new treatments that are coming out and new approaches to therapy. This really offers a lot of hope for the future. Most of the new approaches are taking into consideration a greater understanding of cancer cells and their environment.

One way in which emerging therapies are being incorporated is as alternatives to chemotherapy for patients who haven't been treated before. Another way is to try to incorporate agents to help chemotherapy work better.

Finally, for patients with relapsed disease we're starting to increasingly use alternatives to chemotherapy when it's become clear that chemotherapy is not the answer for those patients.

There are a variety of agents that have been developed to inhibit specific pathways in the cancer cells that are now being investigated in clinical trials. These drugs are designed to interfere with specific biological changes that occur in the cells and that cause cancer to arise. Examples of these include PI3 kinase inhibitors and Bruton's tyrosine kinase or BTK inhibitors.

Another approach is to use agents that target gene expression in the cells and these are known as epigenetic targeting agents. Examples of these include histone deacetylase inhibitors and methyltransferase inhibitors.

A major wave of research at this point involves monoclonal antibodies. Monoclonal antibodies are proteins that are engineered in the lab to bind to specific targets on B cells and B cell malignancies. Another treatment approach that takes advantage of monoclonal antibodies is radioimmunotherapy or radio-labeled monoclonal antibodies. Radioimmunotherapy refers to an agent in which a radiation molecule is attached to a monoclonal antibody and delivers the radiation directly to the cancer cells. Examples of these that are currently available and in use for NHL are I131 tositumomab or Bexxar® and Yttrium-90 ibritumomab tiuxetan or Zevalin®. There are other radioimmunotherapy agents that are being developed, trying to optimize the ability to deliver the radiation directly to cancer cells.

Another approach using monoclonal antibodies are antibody drug conjugates. An antibody drug conjugate is a monoclonal antibody that has a chemotherapy agent attached to it. These are designed to carry the chemotherapy agents directly to the lymphoma. An example of this that's just recently been approved by the FDA is brentuximab vedotin or Adcetris®. This molecule targets a protein called CD30 that's on the surface of a variety of different lymphoma subtypes, including Hodgkin lymphoma and anaplastic large T cell lymphoma, in addition to several other types of lymphoma. It's clearly very effective in Hodgkin lymphoma and anaplastic large T cell lymphoma, where it's been approved by the FDA, and it's being studied for use in other subtypes of NHL.

Other antibody drug conjugates are being developed for use in lymphoma. These are specifically targeting antigens that are more common on B cell malignancies such as CD19 and CD22.

All of the agents that I've discussed are showing a lot of promise in clinical trials and offer a lot of hope for the future.

Lauren Berger:
The Leukemia & Lymphoma Society is committed to providing education, support, and guidance to people living with blood cancer. If you would like more information on what you've heard, or for other education materials or support, we encourage you to contact an Information Specialist at The Leukemia & Lymphoma Society by calling 800-955-4572, or email us at infocenter@lls.org.

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On behalf of The Leukemia & Lymphoma Society, thank you for joining us today. We wish you well.

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