

## LYMPHOMA UPDATE

*from the American Society of Hematology (ASH)*

48<sup>th</sup> Annual Meeting

- RICHARD LUTES, MD:** We're here today at the 48<sup>th</sup> Annual Meeting of the American Society of Hematology in Orlando, Florida. I have the pleasure of speaking with Dr. Hillard Lazarus from Case Western Reserve University. It's good to have you with us, Dr. Lazarus. As our first topic let's start with mantle cell lymphoma [MCL]. For patients with newly diagnosed mantle cell there are at least two studies looking at the use of immunochemotherapy followed by autologous stem cell transplantation. Can you tell us about some of the risks and benefits of this approach?
- HILLARD M. LAZARUS, MD:** Mantle cell lymphoma is a relatively uncommon non-Hodgkin's lymphoma [NHL] accounting for only about 5% of cases, but it's very important because while the people used to think it was very slow growing, we now realize it can be very, very resistant to treatment and it appears that the use of high-dose chemotherapy early in the course of mantle cell lymphoma may be of considerable benefit. These were data that were generated a number of years ago and have been verified with a number of more recent studies including the two you described. In part the addition of immunotherapy, in this case, rituximab, has made the transplant approach much more effective and much safer. Rituximab is a monoclonal antibody like a guided missile that is not chemotherapy, but it seeks out the tumor and spares the normal tissues. These two trials have corroborated the fact that patients with mantle cell lymphoma should be considered for a transplant using their own cells much, much earlier in the course of their disease rather than waiting for the disease to get resistant to treatment.
- DR. LUTES:** There's also a session devoted to the role of immunochemotherapy in treating diffuse large B-cell lymphoma at this meeting, a combination of rituximab and chemotherapy, can you comment on these studies please?
- DR. LAZARUS:** I think this is yet another major advance in the treatment of non-Hodgkin's lymphomas. Chemotherapy is certainly effective, but does not work in every patient and does not work in every patient for long periods of time. The advent of these monoclonal antibodies has been very striking in the sense that not only do these monoclonal antibodies treat the tumor and leave the normal tissues relatively unharmed, but they seem to make the chemotherapy work better and that's one of the things. We now understand that there are certain features of the malignant disease in which the monoclonal antibodies will work synergistically or work together with the chemotherapy to make it more effective. This is true

## LYMPHOMA UPDATE

*from the American Society of Hematology (ASH)*

48<sup>th</sup> Annual Meeting

- DR. LAZARUS:** not only in the slower growing lymphomas, what we call follicular or indolent lymphoma, but clearly in the more aggressive diffuse large cell lymphomas. In fact, as a result of the combination of monoclonal antibody treatments like rituximab with chemotherapy, the whole playing field has been elevated. By that I mean, there used to be what were considered 4 or 5 categories of patients, that is those who had very, very bad disease, those who had bad disease, and those who had relatively better disease. We now have a number of studies that by combining chemotherapy with these monoclonal antibodies, we're now able to compartmentalize the risk groups, in some studies which have been presented at this meeting, to only 3 categories. In general, patients' overall outcome is considerably better than it was less than 5 years ago.
- DR. LUTES:** There's also a study looking at CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone] chemotherapy followed by Zevalin<sup>®</sup> (ibritumomab tiuxetan) in patients who are elderly, can you comment on this please?
- DR. LAZARUS:** This is another variation on a theme. The particular drug in this case, Zevalin, is a family of what's called radioimmunoconjugates. This is when the monoclonal antibody, or the guided missile if you will, that seeks out the tumor and leaves the normal tissues alone is now fused or combined with a bomb; the antibody itself doesn't have to do the job, it does to an extent, but it brings along with it, and delivers, a pay load in the form of radiation. So now by bringing radiation directly to the tumor you can kill the cell more effectively. These studies now which have been presented at this meeting are intriguing. They are small in numbers and the follow-up has been somewhat short, but it's very encouraging and it appears that in select patients, chemotherapy followed by these monoclonal antibodies, in this case the radioimmunoconjugates, are effective. Yes, there's a price to pay, using these radioimmunoconjugates may be associated with more suppression of the bone marrow, that is lowering of the blood counts, making patients more anemic, more at risk for infection, and more at risk for bleeding than just using the naked antibodies like rituximab. Nonetheless, in select patients this may be a better choice than other treatments.
- DR. LUTES:** Also at this year's meeting there have been several presentations looking at predictors of outcomes for patients with diffuse large B-cell lymphoma treated with R-CHOP (rituximab-cyclophosphamide, doxorubicin, vincristine, prednisone), can you comment on some of these studies please?

## LYMPHOMA UPDATE

*from the American Society of Hematology (ASH)*

48<sup>th</sup> Annual Meeting

- DR. LAZARUS:** I think I alluded to this already. There had been some studies from single institutions that reviewed their experience and tried to identify clinical characteristics that would predict patients who would do better versus those who would do worse and the two points to be made here are that these clinical predictors have been very useful, but when adding monoclonal antibodies we seem to make the overall outcome for all patients better. Now we can eliminate some of these very high risk groups and have been able to simplify the different disease groups for patients such that it's easier to understand who's going to do better and who's going to do worse.
- DR. LUTES:** And what are some of the latest developments in transplantation in the lymphoma category?
- DR. LAZARUS:** Transplantation has become much, much safer for patients who have lymphoma and, importantly, the results have become even more effective. This is in part due to a greater understanding of how to use the chemotherapy and how to use the supportive care, which has become extremely effective and sophisticated, in part because of colony stimulating factor or hematopoietic growth factors, the use of blood rather than bone marrow, better antibiotics, but also the use again of monoclonal antibodies. These agents give you more bang for your buck without a lot of side effects and have made the treatment considerably more effective without making the patient sicker.
- DR. LUTES:** Gene expression profiling and microarray analysis have become increasingly important in hematology/oncology, can you discuss any new findings at this meeting in this area please?
- DR. LAZARUS:** Yes, this is a very complicated area. There are genes within our body that are involved in the regulation of all of our tissues, that is there are genes that act like a gas pedal and a brake—signals for tissues to grow and signals for tissues to stop growing or shrink down and to unravel the mystery of all these genes has been quite a task. There are a number of ways of approaching this. The simplified way of looking at this is to take a biopsy from each particular patient and to make a distillate of the tumor and put these genes on a slide, then there are ways of looking at the genes to see whether they're on or they're turned off. And our understanding now is advanced to the point that there are what are called target genes.

## LYMPHOMA UPDATE

*from the American Society of Hematology (ASH)*

48<sup>th</sup> Annual Meeting

**DR. LAZARUS**

In patients who have malignant disorders there are genes that we want to turn off to keep the lymphoma from growing, and there are genes that we want to turn on to help the immune system get rid of the lymphoma. So there is a whole category of these approaches and as you've described if we can start to figure out how to harness the different genes this is a big target, but there are small molecules and other kinds of treatments that may go after one class of gene or another class of gene and we're now really beginning to understand this. And I think the future is that in the next several years we'll start administering various drugs based on what we see in an individual patient's biopsy, which is probably the best way of approaching tumor on a case-by-case basis rather than in a global fashion.

**DR. LUTES:**

To wrap up, if I'm a patient with lymphoma can you give me, you've already touched upon it, but what might I see in the next 3 to 5 years in my therapy?

**DR. LAZARUS:**

That's a real tall order. I think that I would first make a pitch for a patient who has cancer of any kind to get a second opinion if you're at all uncomfortable with your care – or just want more information. We in the profession expect this and I think that there is considerably greater benefit if a patient is able to do this, if there's sufficient time, which is not always the case. Secondly, I think that the field has now integrated from what we call clinical approaches, that is in years gone by just examining a patient and talking to a patient would be the old version, then with the advent of sophisticated testing like CT scanning we were really able to understand where the disease was and how it's behaving.

In this meeting and in previous meetings various investigators have shared data with us that look at even better ways of imaging of the patients to know where it is and whether it's active or not. And this is very important because some people may need more treatment and they're not going to get it with less sophisticated testing and other people clearly may have gotten plenty of treatment and don't need any more.

One major advance that has been developed and again is being refined as presented at this meeting and in the next few years, is what's called a PET scan. And this is really, I think, beginning to revolutionize our understanding of when people need treatment, when we can stop treating and when people are at particularly high risk. So it's not just the treatments themselves, but understanding when to treat and when not to treat. I think that's important, as

## **LYMPHOMA UPDATE**

*from the American Society of Hematology (ASH)*

48<sup>th</sup> Annual Meeting

- DR. LAZARUS:** well as the understanding of how to better combine treatments for various patients, that is individualizing the treatments. This treatment would be better for this patient versus another treatment would be better for another patient.
- I think that's what we're getting at and I think in general in the field of lymphoma we have made considerable advances. There are clearly people who have benefited and who are alive today, but there is still a lot of work to do and I think that the use of more potent treatments such as transplantation for more aggressive disease, administered early in the course of the disease, may be what we need to see happen in the next several years.
- DR. LUTES:** Doctor, we want to thank you very much for joining us today and giving us your time and this excellent information.
- DR. LAZARUS:** Thank you.