News from ASH: Updates in Lymphoma Research
ASH Conference Coverage
December 6, 2008
Stephen Schuster, M.D.

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Introduction

Andrew Schorr:
Hello. This is Andrew Schorr broadcasting from the 50th annual meeting of the American Society of Hematology in San Francisco this year where news continues to be made in blood related cancers and some other blood related conditions as well.

In this program we are talking about lymphoma, and our guest expert is Dr. Stephen Schuster from the University of Pennsylvania in Philadelphia where he is at the Abramson Cancer Center. He is a lymphoma expert. Actually are you the director the lymphoma program there doctor?

Dr. Schuster:
Yes.

Andrew Schorr:
Okay. Thank you; the perfect guest for us. So sir there have been lots of changes going on in different lymphomas, and each year we say, ‘Well it’s an exciting time.’ How do you describe it this year?

Dr. Schuster:
I think each year is increasingly exciting, and the excitement grows in a logarithmic fashion each year, and I think this year is more exciting than the last, and it’s been that way for some years now. I think this is just a very exciting time to be working in this area.

Andrew Schorr:
Okay, now of course we’re not just talking about one disease. We have different forms of lymphoma. So help us, maybe let’s break it down a little bit. What’s sort of hot here either for new therapies now or ones that are very promising and how they apply to some common lymphomas?
Dr. Schuster:
Yes you’re right, exactly right. Lymphomas are a heterogeneous group of diseases that have their own unique features and similarities as well, and in terms of our therapeutic approaches there are differences for each lymphoma specifically, but also similarities that run along the similarities among the diseases themselves. I think the greatest impact over the last eight years has been the introduction of immunologic approaches to our traditional chemotherapeutic approaches. These have really changed in a fundamental way the types of outcomes that we have when we treat patients with lymphoma.

I would say that we had, there were several major periods of development in the treatment of lymphomas I’d say in the late 1960s and the early 1970s with the development of combination chemotherapy at the National Cancer Institute and the demonstration that we could have long term disease-free survivors which was a new thing in what at that time was called diffuse histiocytic lymphoma, now called the diffuse large cell lymphoma or diffuse large B-cell lymphoma.

That was a breakthrough. That was in the early 1970s. We juggled drugs around for about the next 20 years, and didn’t make much progress. There were a fraction of long-term disease-free survivors. We certainly benefited many patients who were symptomatic or needed treatment and improved quality of life with that therapeutic approach, but it wasn’t until the late 1990s or early 2000s with the addition of immunologic approaches to chemotherapeutic approaches that we made an incremental advance in cure, in curing patients.

Just as the early chemotherapy regimens were a paradigm for development of that approach, the application of monoclonal antibody therapy for example, rituximab as the first FDA approved antibody in the late 1990s for treatment of B-cell non-Hodgkin’s lymphomas has created a second paradigm, and that is the addition of immunotherapy to chemotherapy, and our results which we now, we have 10 years since the introduction of Rituxan, we now see the impact of immunotherapy to chemotherapy, but what’s exciting is, and this is something we didn’t have back in the 1980s and early 1990s, is the diversity of immunologic approaches that are being developed.

The chemotherapy works by a number of specific mechanisms, antimetabolites, alkylating agents or what have you. The immune system is infinitely more complex, and what we are doing now is mimicking the activities and functions of the immune system to treat tumors of the immune system. So antibodies, your immune system, your lymphocytes make antibodies to fight infections, to neutralize toxins to protect you from the environment. Well we’ve made an antibody that treats B-cell lymphoma cells.

Now there is plethora of antibodies that are being tested, and at this meeting, particularly Monday, we are going to hear updates on some of the newer antibodies that are, some are second and third generation Rituxans that have different binding affinities and different potential applications, antibodies to other antigens on B-cells, antibodies that
work by mechanisms that are quite different from each other, some focusing on using complementism, focusing on trying to recruit other immune cells to the sites of lymphoma as their mechanism of action. So we are exploiting multiple antibody-mediated mechanisms.

Cellular therapy is the other big thing. So the antibodies represent one immune system approach to host protection. The other is cellular immunities, T-cells largely and natural killer cells. Well so-called adoptive immunotherapies being developed, autologous T-cells are taken from patients and can be used to restore the immune system after chemotherapy as well as to enhance anti-tumor responses. I mean I could go on and on.

Andrew Schorr:
Let me go back over that a little bit with you. So we had the sort of chemotherapies that were kind of howitzers firing at the cancer cells, and then we developed targeted therapies monoclonal antibodies. I actually received Rituxan as part of my CLL therapy trying to target the B-cells, so kind of a cruise missile for a certain cell type, and now you say you have second and third generation cruise missiles, if you will, looking for the target.

Dr. Schuster:
There are hitting other targets on the same cell is the way to think of it.

Andrew Schorr:
Okay, to try to give it one-two or even a one-two-three punch to make sure it’s out, and then you are talking about well the best thing of all would be if we could have your immune system spot cancer cells that it missed the first time around, and what I’ve been hearing about is some therapies to knock back the cancer to a very low level and kind of turn on those T-cells again and say, ‘Look you missed it the first time. There is some mopping up to do. Go do it.’ Did I get it right?

Dr. Schuster:
You got it right, exactly right, and chemotherapy is very useful, but as I said the addition of immunologic approaches has vastly improved outcome and the quality of the responses that we can achieve. We’re going to take that to the next level, and rather than just passively administer immunologic agents to patients to help, we are going to try to strengthen their own immune system to continue to combat any residual lymphoma that might be present, and even to promote the health of the immune system in general.

Andrew Schorr:
Your own surveillance.

Dr. Schuster:
Yes.
New Therapies and Treatment Options

Andrew Schorr:
Now question. You alluded to it. There is a study being presented Monday, there was just a news conference about it, about an oral therapy. So a lot of people, and I’ve been through it myself, chemotherapy and get poked and prodded and all that. So it’s obviously what the drug is depends on how it would be metabolized, how you deliver it. So that’s kind of encouraging too if there actually may be even new pills you could take.

Dr. Schuster:
Yes, well I’ll tell you what’s really interesting. So we are talking about cells and antibodies. These are things that are generally administered by vein but by the way are much more easy to tolerate than cytotoxic chemotherapy, but there is a new generation of therapies, again targeted would be the best way that we can group this therapeutic approach, with the I would say the immune system mimetics that we’ve been using, and these drugs actually target intracellular pathways that are actually part of the way the immune system functions.

So okay, we’ve worked to mimic the two arms of the immune system, the antibody and cellular immune system to create anti-tumor immunity to enhance our chemotherapy effect. Now what we have also done is we’ve learned about intracellular signaling pathways that are responsible for cell growth and cell death in immune system cells. Okay? And we have targeted those pathways and are using that to treat lymphomas.

For example what may be a crucial signal for activation of a B-lymphocyte when it sees its cognate antigen as being, you know it’s sensing from the instructions from the environment to do what it is supposed to do, will involve transmission from the surface of the cell to proteins inside the cell, a signal. It turns out that a lot of B-cell malignancies, a lot of lymphomas are the result of aberrations of those signaling pathways.

Andrew Schorr:
Noise in the channels.

Dr. Schuster:
Yes. So what’s really exciting over the last few years has been a greater understanding of those pathways. One of these we were talking about earlier is the Syk kinase, or the spleen tyrosine kinase agent, and these tyrosine kinases are signaling molecules in cells that usually can go on and off in normal cells, but are on and over expressed in the malignant cells and are part of the malignant process. Well you’re right. Oral pills that are small molecules that target those specific pathways which are very important for lymphoma cells, and in fact when these agents block them we have a therapeutic effect, the lymphoma cells die, the normal lymphocytes can actually generally survive for a period of time with that kind of inhibition, and again the drugs have, you are on an
intermittent exposure schedule, but it seems to be your normal immune system can tolerate some intermittent inhibition of these pathways, but they are vital to the survival of lymphoma cells, and interruption leads to cell death and response.

So now we are targeting the immune system by understanding the inner workings of the immune cells themselves. So the antibodies work on the outside surface of lymphoma cells. Even T-lymphocytes work on antigens and targets on the outside. The next class of agents we’ll be seeing in widespread application target proteins on the inside of the cell, and come from an understanding of how the these <inaudible>

**Andrew Schorr:**
Okay, so we, as patients, we’ve been going to medical school a little bit here. So the bottom line though is that deeper and deeper, right into the heart of the cancer cells now you are understanding not only how to target them on the outside, but how to get involved in the communication or miscommunication on the inside. So what does that mean then to a lymphoma patient, knowing everybody is different and they are different, but generally for folks let’s say in Pennsylvania where you are, what hope does it offer them now?

**Dr. Schuster:**
Well I think, let’s put this into perspective. Okay? Cells and organisms are very adaptable. I mean, the reason we were able to survive for thousands of years as a species is because our cells can repair themselves and get around injuries or interruptions in their processes as a result of environmental insults, and this is how cancers can survive. They can get around single agent insults.

**Dr. Schuster:**
Yes. That’s why combination chemotherapy worked better than chemotherapy with single agents. Well what I’m telling you now is that we not only the conventional cytotoxic agents, which have been active, we have ways of treating cells using humoral immunity, using cellular immunity and targeting intracellular pathways. So I’m telling you that if we can hit these cells at enough spots simultaneously, combination therapies, I think you are looking at a high probability of success if the past tells us anything, and I think it does. History generally is worth looking at.

**Andrew Schorr:**
You’re pretty passionate today.

**Dr. Schuster:**
That happens when you come to this meeting and you hear what’s going on. I’ll be charged up for months after this I have to tell you.
Andrew Schorr:
Well it sounds like for the benefit of many patients, and I know they are very grateful for the work you do at the Abramson Cancer Center at the University of Pennsylvania. So I’ll let you go to; doctors I have to tell you folks, like have track shoes running around a huge convention center, and there are meetings that go on from early in the morning until late at night. So Dr. Stephen Schuster from the University of Pennsylvania, Abramson Cancer Center, thank you so much for being with us on Patient Power.

I’m Andrew Schorr broadcasting from the 50th annual meeting of the American Society of Hematology in San Francisco, and I like to tell people that knowledge can be the best medicine of all. Thanks for joining us.