

State-of-the-Art Treatment for Lymphoma

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INTRODUCTION

Andrew Schorr:

Hello, and welcome once again to Patient Power on the website of the Seattle Cancer Care Alliance. We're delighted we can do these programs every two weeks and connect you with Seattle Cancer Care Alliance experts and bring you the latest in cancer information. Today we are going to talk about lymphoma. We certainly have an expert to visit with on that score, and that's Dr. David Maloney. Dr. Maloney is a hematologist oncologist, and he is an associate member of the Clinical Research Division at the Fred Hutchinson Cancer Research Center in the Seattle Cancer Care Alliance. He is also an Associate Professor at the University of Washington. Dr. Maloney, welcome to Patient Power.

Dr. Maloney:

Thank you very much Andrew, it's my pleasure to be here.

Andrew Schorr:

Thank you sir. When we talk about lymphoma and someone gets diagnosed with lymphoma maybe they are not familiar with it. I know it's not just one disease. Could you give us the high level view of what is lymphoma and the different types?

Dr. Maloney:

I think that's a really key point. Lymphoma is a cancer of the lymph system or the immune system. It's really important to realize that not all lymphomas are the same and in telling someone 'Well I have lymphoma' has very, very different meanings and outcomes potentially based on what type of lymphoma you have. The first important thing is to find out what exact type of lymphoma it is. There are several different classification systems that try to enumerate exactly what type of lymphoma it is, and there are probably 17 or 18 different types of lymphoma but they can really be broken down into three major categories that affect most patients. There are a lot of outliers, and so it's important if your type of cancer is not one of the three we are talking about that there is still a lot known about that type of lymphoma. It's just that it is a little more rare disease.

So the three basic types of lymphomas are those that are considered aggressive lymphomas and those that are considered indolent lymphomas and they have different features and different points that affect therapy. For example, the aggressive lymphomas

are lymphomas that we generally don't observe patients for. We really want to get people into treatment as soon as possible because that treatment can actually be curative, and it's important that you get that therapy.

In contrast there are other lymphomas like indolent lymphomas where the exact timing of therapy is not as important, and we will often observe patients for a while before they reach a point where they need to be treated. The management of those patients is a little bit different. So, it's important that you understand what type of lymphoma you have. The words that are important are like "diffuse large cell lymphoma" or "mantle cell lymphoma" or "follicular lymphoma." Those are the big three, and we'll talk about those today.

State of the Art Diagnosing and Treating Large Cell Aggressive Lymphoma

Andrew Schorr:

Let's start by talking about the large cell more aggressive lymphoma. Where are we with sort of state of the art treatment today?

Dr. Maloney:

In general the state of the art therapy for this disease consists of first having the diagnosis made by a lymph node biopsy, and wherever possible we really like that to be an excisional biopsy where the biopsy is actually taken out at an operation so the pathologist can examine it. In cases where we can't do the biopsy then sometimes we can do them with CT guidance or needle biopsies, but it's almost always better to have a full excisional biopsy if possible.

The second key thing is that that biopsy needs to be read by a pathologist that is a hematopathologist, one who is an expert in lymphomas. If you are at a center where that doesn't happen then the sample should be sent to an expert hematopathologist such as those we have here at hematology division here at the University and at the SCCA .

Once you have the diagnosis, then large cell lymphoma is a disease where it is really important that we do very good staging. Patients undergo a thorough physical examination and usually some scans, CAT scans or PET scan, and usually a bone marrow biopsy. That can tell the extent of the disease. In aggressive lymphomas it is very important to determine the extent of the disease and some other characteristics about what the patient's performance status is and a few other laboratory tests. That can give a prognostic index called the International Prognostic Index that can really aid in giving the patient some kind of idea of how successful the therapies will be.

In almost all patients the therapy is usually chemotherapy and the most standard regimen that has been settled upon in most centers is now a combination of CHOP, chemotherapy plus rituximab, and that is usually given for three to six cycles or sometimes a little longer and may or may not be followed by some radiation. That's really the state of the art in aggressive lymphomas. Depending upon the extent of the disease and some of those

pretreatment characteristics we are able to cure somewhere between 30 and 90 percent of patients, again depending on those factors.

There have been a lot of studies now that have shown that the addition of the antibody rituximab to the chemotherapy improves the cure rate and the survival rate of patients with this disease. This is a relatively new finding in the last seven to eight years and has really revolutionized the therapy for this particular disease.

Andrew Schorr:

If someone had this CHOP-R, let's say not at the SCCA but somewhere else and then they were failing, is there anything you could do for them at the SCCA that you've had some luck with?

Dr. Maloney:

This type of lymphoma we always try to cure it at the beginning with aggressive therapy such as Rituxan plus CHOP or a very similar treatment. If it comes back or if that doesn't work, it doesn't go into complete remission, then for patients under the age of about 70 where standard of care is to try to do a more aggressive therapy with a different type of chemotherapy regimen and then collect stem cells from that patient or bone marrow cells from that patient and then use those in what is called high-dose therapy and autologous transplant. This treatment can then cure a good portion of those patients who were not cured by the initial chemotherapy. Here at the SCCA we have a number of protocols utilizing some innovative additional drugs to try to make those treatments work better.

Diagnosing and Treating Low-Grade or Indolent Lymphoma

Andrew Schorr:

Let's move on to the flip side. We have the large-cell aggressive lymphoma and then we have the follicular low-grade lymphoma that you often refer to indolent. It's not aggressive, but yet it affects a lot of people with lymphoma. What do you do there?

Dr. Maloney:

It's very similar to the aggressive lymphomas in terms of the first workup of the patient. In fact almost all lymphomas get that initial same workup. Again it's critical that the biopsy be reviewed by an expert hematopathologist who can give a definitive diagnosis. It makes a big difference of whether it's a follicular lymphoma or whether it's a diffuse large cell lymphoma. The implications for both long-term results and what you do and the timing that you do them are key. So for a follicular lymphoma patient, we would again look at the extent of the disease and also determine whether the patient is having a lot of symptoms.

Typical symptoms that patients can have include fevers or night sweats, unexplained weight loss, and sometimes patients can have large lymph nodes that are actually pushing on another organ and causing problems. Any of these kinds of findings would be a reason to initiate therapy. In contrast to the aggressive lymphomas though if people just have small lymph nodes or lymph nodes that aren't causing any problems maybe it's just an incidental note that someone has had a lymph node for a number of years and then finally gets it

biopsied and now they are told they have follicular lymphoma, and we can't find very much of it elsewhere. Those patients can be managed by watching carefully where we actually delay the therapy until they actually have a symptom that needs treating.

The treatments themselves are often very similar to what would be given for an aggressive lymphoma, but there is also a lot more variety, and there is no one right answer. In fact I think one of the biggest controversies right now in the whole field is what should that first chemotherapy be? The only data that we have so far is antibody rituximab should be likely added to that first chemotherapy. So chemotherapy such as the CHOP regimen or a fludarabine-based regimen or others, CVP for example, can all have the rituximab added to them, and there have now been four or five studies that have proven that addition of the antibody to the initial chemotherapy improves the outcome including improving survival in some patients.

The initial treatment is usually with chemotherapy plus rituximab, and that's given until people go into remission and then they are usually followed to see how long they will stay in remission. Now unfortunately unlike the aggressive lymphomas where there is a real chance of curing the patient with the first treatment, with follicular lymphomas the teaching is that they invariably come back, and if you watch long enough and often patients will have the disease come back, and they will need other treatments. Some of the current really hot topics in this field are does it matter what the first chemotherapy is? One of the big studies we are doing here in Seattle as well as in the whole United States is the Southwest Oncology Group Trial S0016. This is a study of using CHOP plus rituximab versus CHOP followed by a radiolabeled antibody tositumomab or BEXXAR, and that study is nearly completed, and we are hoping to see eventually results and see whether the addition of a radiolabeled antibody, which is similar to Rituxan, but it now carries internal radiation essentially, whether that will make CHOP chemotherapy better than R-CHOP, Rituxan added to CHOP chemotherapy.

Andrew Schorr:

Let me just jump in for a second to help people understand that. We talk about the chemotherapy drugs that kind of, not a shotgun approach, but sort of broad, it's almost like an antibiotic-like broad spectrum. Then you have the monoclonal antibody that is really focused on the type of cells that are likely to be cancerous, usually B-cells in this case. Is that right?

Dr. Maloney:

Right. So the rituximab is what I call a naked antibody, or it's an antibody that is cloned to just go against CD20. It's like a normal antibody in your body but it's now turned against B-cells, against this target that is called CD20, which is on all the lymphoma cells.

Treatment Utilizing Radiolabeled Antibodies

Andrew Schorr:

Then we've got the later drug you were talking about, the radiolabeled antibody that's like that targeted but it takes a little bomb with it to try to kill that cancer cell, right?

Dr. Maloney:

Exactly right. That we can kind of consider more like the guided missile approach, and so the antibody part of it brings that radiation and concentrates it at the site of the tumor so that when that radiation decays then hopefully it will kill the tumor more than causing damage to the rest of the person. Radiolabeled antibodies have a lot more potency than plain naked antibodies, but they are also a little more toxic. They can have effects on the bone marrow, which we don't really see with some of the naked antibodies. There are currently two of these antibodies available; one called BEXXAR or I-131 tositumomab and one called Zevalin that is yttrium-90 ibritumomab tiuxetan. They are both excellent products that have high response rates in follicular lymphoma.

Andrew Schorr:

So my question is that you have a study going on to see if you use BEXXAR and is that helpful for people as part of the initial treatment, but in either case whether they have had the CHOP-R or the other chemotherapy regimens with Rituxan or even part of this study, are there places for the radiolabeled antibodies now where they are approved, where they fit in? Also what about your new techniques with transplants for people where their lymphoma comes back?

Dr. Maloney:

From the perspective of the approved uses of these radiolabeled antibodies, both of these products are approved for patients who have failed primary therapy or failed therapy with rituximab-containing regimens. Both have been approved with very high response rates, over 80 percent of patients going into at least partial remission from a single treatment with these antibodies. They are widely available for that although they are not widely used. This has to do with some issues of reimbursement, and so it's somewhat complicated, but we are hoping that that is going to improve.

That study I was referring to is a new approach that is trying to use the antibody in first remission to see whether it can deepen the remission and improve the outcome the chemotherapy alone. There was some data presented at ASH this year using the Zevalin product after chemotherapy, which showed that it did in fact prolong the time to progression in those patients who received the radiolabeled antibody compared to the patients who received observation. We think this is very exciting. Hopefully the results from the SWOG trial will mimic what we saw in the other study. We'll just have to wait and see.

Transplant Therapy for Indolent Lymphoma

Andrew Schorr:

Let me just tell folks, ASH stands for American Society of Hematology. That's Dr. Maloney getting together with all his peers around the world. We'll get back to see if there is anything coming that also looks promising. That meeting just happened a week or so ago. There is always a lot of data presented there. Dr. Maloney related to this indolent lymphoma, follicular lymphoma we talked about looking at studies of 'can you make that first-line treatment more powerful?' If people fail that then, I know the Fred Hutchinson Cancer Research Center has always pioneered transplanting and you refined that tremendously. Does that have a role for these indolent lymphomas?

Dr. Maloney:

It sure does. Just like the aggressive lymphomas were, it's actually standard of care to do transplants. In the follicular lymphomas it's not maybe quite standard of care, but it is my kind of next therapy if people have a relatively short or poor outcome from standard treatments then I certainly encourage them to consider this earlier. Again the approach is typically by collecting the patient's stem cells and then giving high doses of chemotherapy or chemotherapy plus radiation and then giving them back their stem cells to rescue them from that toxicity and then hopefully then be able to eliminate the tumor. That's a standard approach again, and we have considerable experience with that here at the SCCA.

In addition, though, we are always trying to learn better ways to do it. One of the most exciting areas is a study led by Dr. Gopal and Dr. Press. Dr. Press is using high-dose radioactive antibodies essentially like the BEXXAR or Zevalin but now in very, very high doses where you have to give back stem cells to recreate the bone marrow. This turns out to be extremely effective in these types of lymphomas and might even keep people in continuous remission for many, many years. I hesitate to use the word 'cure' but we do have patients out many, many years now that appear to be potentially cured after this type of approach. I am very excited about that.

Now let me just add one different thing and that is if people don't have that kind of a transplant and still it comes back, then we have very exciting data where you can use a different type of donor. Instead of your own stem cells you can use a HLA-matched donor. That's a donor that matches your tissue type either from a family member or an unrelated donor. Those transplants can also be remarkably successful and in contrast to the other treatments where people seem to keep relapsing, people seem not to relapse after these transplants if the transplants are successful. So they are higher risk, but we are doing a large number of those in people who have kind of run out of other options. It's always something to think about.

Andrew Schorr:

It sounds like that at the SCCA you have several lines of options for people as you know exactly what you are dealing with with the biology of their lymphoma type.

Dr. Maloney:

Yes we certainly do and I think the most important thing for anyone who has been diagnosed with lymphoma is to establish a really good rapport with your oncologist and to realize that you need a broad picture of the whole treatment plan because there are some things that you can do first, which will close some doors later on or make things not possible. It's always wise to be thinking along the whole big picture once you have this diagnosis.

Andrew Schorr:

Right, a road map. If you need additional treatment what would it be and to consider whether the first treatment that's been suggested will preserve your options or whether they will close them. That's a very important discussion. I always tell people, let's say if they are listening somewhere worldwide but maybe some of these options at the Seattle Cancer Care Alliance could come into play, then there is no problem in getting a second opinion or consultation early on so that you have folks like Dr. Maloney, Dr. Press, Dr. Gopal, etc. play a role as sort of helping be an architect of a long-range plan should you need it.

New Approaches for Treating Mantle Cell Lymphoma

Andrew Schorr:

Let's talk about one other type of lymphoma and that's mantle cell. I know it's not common, but there have been changes there too, and you see that at the Seattle Cancer Care Alliance. Help us understand where we are there with treatment.

Dr. Maloney:

Mantle cell lymphoma is a relatively rare disease. It only represents about five percent of lymphomas, but it is particularly challenging. It kind of has the worst components of both of the indolent and aggressive lymphomas. It tends to be aggressive and people have a relatively short survival with standard treatments, but it also tends to keep coming back even though we give very aggressive treatments. This disease does respond to our traditional treatments such as R-CHOP chemotherapy, but they tend to be relatively short-lived, and most patients relapse within a couple of years. The newer approaches are to use transplants, autologous transplants, in first remission after that chemotherapy. That's what most of our series are focusing on as options for patients.

An alternative was presented from the M.D. Anderson Cancer Center where they use a more aggressive chemotherapy regimen called rituximab plus hyper-CVAD chemotherapy. This is a very aggressive treatment that does require multiple days in the hospital for each cycle, and it's very rough on patients, and it's pretty much limited to people under the age of about 60. When that can be used, it does seem to be more effective rituximab plus CHOP chemotherapy, and we're utilizing that in some of the younger patients but also still then considering transplants. For people who relapse, then the allogeneic transplant using non-myeloablative conditioning, as I mentioned before for some of the indolent lymphoma patients, has also proven to have surprising efficacy, and many patients are in long-term

remissions and appear to be potentially cured, which is something we would generally not see with other approaches. That is always an option, again, to consider should the other treatments fail.

News from ASH 2007 on Transplant and Radiolabeled Therapies

Andrew Schorr:

I know we are talking about different diseases under this category of lymphoma, and you can comment on any subtype you like, but we just had this big meeting with almost 22,000 people from around the world, the American Society of Hematology meeting. What do you come away with that you are excited about or impressed with that you think can make a difference to people now right away?

Dr. Maloney:

I think one of the key findings in my area that I was interested in is that we presented results as the M.D. Anderson presented results showing that the remissions that patients can have with follicular lymphoma or the indolent lymphomas or even with CLL after allogeneic transplants, these non- myeloablative allogeneic transplants can be extremely durable. Patients appear to have extremely low risk of relapsing afterwards. The biggest question is what is the best timing for that kind of transplant because they do still carry risk of graft-versus-host disease and infections, which can cause people to die for reasons other than their lymphoma and makes it somewhat risky. So you need to eventually come up with a point where you decide what's the best timing of that kind of an approach? Where is the risk versus the benefit going to be the best? The M.D. Anderson Group presented some data using the transplants earlier with outstanding results, and we presented some data of people who had already failed other transplants, which also had very good results. I think the field is really rapidly realizing that this is a new treatment that should be offered to patients at some point.

The other thing that I was again struck by was the use of the radiolabeled antibodies, and the one study that I mentioned before showed that in follicular lymphoma patients that this did add to the duration of outcome of the first treatment. I think we need additional data, and we need to see the full papers. These are only 15 minute presentations, so you can't get the full data in just that quick a time, so we are eagerly awaiting those studies.

Improvements in Transplant Therapy

Andrew Schorr:

Dr. Maloney let me ask you about this. You used this term non-myeloablative transplant, allogeneic transplants. So donor cells non-myeloablative were different from the way you've done it traditionally where you kind of quite frankly radiated the people and blew away their existing immune system even though it was damaged. Now you preserve some of their immune system and then, as I understand it, the donor immune system comes in and fights, and the donor immune system wins, and hopefully you cure the disease in the process. Where are we with what age a patient can be? It used to be pretty restrictive. Has that changed?

Dr. Maloney:

Yes that has totally changed, and Andrew I think those are great points. The way we've traditionally done allogeneic transplants, and again that means transplant of bone marrow or cells from another person that is not an identical twin, was to give very high doses of chemotherapy with or without radiation. That would essentially eliminate the bone marrow, and then you give the donor bone marrow from the other person. It would set up shop and replace the bone marrow, and you would then recover, but that was highly toxic and associated with a lot of complications. Because of that, the age restrictions were generally below 50 for that kind of an approach.

About 10 years ago, studies both here and at M.D. Anderson realized that we could do transplants with much less conditioning or much less treatment. So, now patients receive one-sixth of the dose of radiation and small doses of a drug called fludarabine, and all that does essentially is essentially paralyze the patient's own immune system so that they cannot reject the donor. Then the donor cells are given, and that donor immune system starts growing in the patient, and it can recognize differences between the person it came from and now the patient. It can actually immunologically attack those differences. What the new donor immune system does is actually eliminate the bone marrow and set up its own shop and in the process hopefully eliminates the underlying problem, the underlying malignancy that we are transplanting the patient for.

This has turned out to be remarkably successful for the lymphomas, for CLL and mantle cell lymphoma and follicular lymphomas in particular where this seems to be able to eliminate the disease. As a consequence the actual toxicities of the transplant are much less because we are not giving that high amount of chemotherapy and radiation. Thus the age range has gone up dramatically to where we have transplanted patients in their mid-70s.

Finding a Donor for Bone Marrow Transplant

Andrew Schorr:

That's very, very encouraging. Now, what about finding a match because we're talking about somebody else's cells. So if somebody is listening and wherever they may be in the world they have their brothers, siblings or close relatives type. What if they don't find a match? I know it is difficult in some ethnic groups, but just generally, where are we now with finding a matched unrelated donor? Also if you would comment about if there is any place where these cord blood cells are even experimentally playing a role?

Dr. Maloney:

I think that is a key element that people get very confused about because it is kind of a bewildering array of possibilities. The first place to start is that we always like to look within the families. If you have brothers and sisters who share the same parents as you then they have a chance of matching your HLA type. There is about a one in four chance that any

one of them, again if they have the same parents as you do, would be identical at their HLA type. If you have one there is about a 25 percent chance and if you have four then it's getting closer to finding a match. That's where we always start. We always start to look at the family.

If you don't have a donor in the family then we generally will try to find a perfectly matched unrelated donor. This takes advantage of millions of people who have supplied samples of their blood to be tested and joined the volunteer registries. With those millions of potential donors, we can type the patient and determine their tissue type and then look and see whether they will just coincidentally match one of these millions of donors that are in the system. Depending again on your background, that can be extremely successful. It's more limited when we get into some of the ethnic groups, and that's the big focus right now of the unrelated donor registries to try to improve the number of donors from the various ethnic groups, but again we can usually find an appropriate donor for someone from the unrelated donor registry.

If that doesn't work then we can look for slightly more mismatched donors either in the unrelated donor registry or even look for cord bloods and that's a very rapidly evolving program. We have a very active program here with Colleen Delaney, M.D., who is utilizing cord blood transplants for many of these malignancies, and there is a good chance we can again find a cord blood.

Lastly if we can't even find a cord blood, then we can often find what is called a haploidentical transplant. This is someone who only half matches your bone marrow type, and that could either be a child or even a parent. Often we can do successful transplants with that. So there are many, many options. It's obviously a bit bewildering to try to figure them all out, but we go through them in a systematic approach.

Andrew Schorr:

Obviously at the SCCA you concentrate on this in a very specialized way as you develop new options for people. To me it sounds very encouraging, but as we come to the end of our program, Dr. Maloney, how do you feel about things? You've been at this a while. It sounds like you have a lot to talk about. It varies by lymphoma type, and I understand how critical it is for a patient to have their cells looked at by an expert pathologist to really first know what you are dealing with, but in many of these areas it sounds like you are making progress and that the SCCA has more options for people.

Dr. Maloney:

That's absolutely true. I am very, very encouraged. I've been in oncology since the mid 1980s or so with my schooling at Stanford, and in those days we showed survival curves for example for patients with follicular lymphoma that had not changed in 30 years. For the first time in history in the last 10 years we are seeing steady improvements in survival in patients, for example, with follicular lymphoma and in patients with large cell lymphoma and in patients with mantle cell. Looking even at the SEER registry data we are seeing steady stepwise improvements as this newer technology has revolutionized our therapy.

One of the most important ones has been the development of rituximab and the other antibodies, and this is just going to continue to explode and improve survival of patients.

Lastly our transplant data I think has really revolutionized the ability to offer these transplants to patients who are in a more similar age range to their actual diagnosis so we are not just treating the youngest people for example. We can actually offer these treatments to people in their 60s and 70s where the peak of this disease really is.

Andrew Schorr:

Yes, and I think one other point for people too is with the more targeted therapies that you're using come often fewer side effects. So you still are treating the diseases more aggressively but often in a more targeted way and so people can often live better during treatment.

Dr. Maloney:

Yes, an excellent point.

Andrew Schorr:

I'm learning. I'm delighted to do these Patient Power programs every two weeks with the Seattle Cancer Care Alliance. Dr. David Maloney, I want to thank you and your team, your colleagues there, Dr. Press and others for your dedication in the treatment of the lymphomas, and we wish you all the best with your continued care for people and working with those of us in the community in advancing care. Let's hope for cures all the way around.

Dr. Maloney:

Yes, thank you Andrew. It's a pleasure talking with you as usual.

Andrew Schorr:

Thank you. Just as we wrap up, I want to remind people that the Seattle Cancer Care Alliance is encouraging women to access the latest technologies in mammography. There is a "mammovan" going around because a lot of women have not always had their annual mammogram. If you want to find out about that the phone number is 206-288-7800 or visit www.sccamammography.org.

By the way, Dr. Maloney, before I let you go is there a phone number people should call related to finding out about lymphoma care at SCCA?

Dr. Maloney:

There is an intake office where we have a whole bank of people that can put you in contact with the right person. That phone number is in Seattle 206-288-1024, and they can put you in contact with one of the lymphoma coordinators who can either schedule a consult with one of our lymphoma docs or another physician.



Andrew Schorr:

Okay. On our next program I'm excited about, and Dr. Maloney you'll have to tune in, on January 9th we are going to talk about state of the art treatment for leukemia and maybe a little bit more review of lymphoma with Dr. Fred Applebaum one of the leaders at the Fred Hutchinson Cancer Research Center and the SCCA.

As always knowledge can be the best medicine of all. I'm Andrew Schorr, and you've been listening to Patient Power brought to you by the Seattle Cancer Care Alliance.

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