Managing Hodgkin Lymphoma Expert Interview Series

A Global Perspective on the Current State of Hodgkin Lymphoma Care

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Editor's Note:
The treatment of patients with Hodgkin lymphoma (HL) is one of the major success stories in oncology. Currently between 70–90% of treatment-naïve patients are cured of their malignancy depending on clinical stage and risk factors.[1] In patients with refractory or relapsed disease, high-dose chemotherapy (HDCT) followed by autologous hematopoietic stem cell transplant (HSCT) is the standard of care, and can lead to a cure in ~50% of patients.[2] However, current combined modality treatment regimens for first diagnosed HL patients can induce severe, life-threatening treatment-related side effects, which include secondary cancers and cardiovascular disease. Despite success in both treatment-naïve patients and patients with refractory or relapsed disease, new treatment options are needed. On behalf of *ManagingHodgkinLymphoma.com* (MHLC), George Davatelis, PhD, spoke with Volker Diehl, MD, director emeritus, internal medicine, University of Cologne in Cologne, Germany, to gain his perspective on the current state of Hodgkin lymphoma care on a global level.

MHLC: *In the general sense, what do you think are the commonalities or the shared needs among the different regions of the world?*

Dr. Volker Diehl: The first thing is a better understanding of the biology of Hodgkin, which means the pathogenesis, the immunology, and the pathology. The most important thing is that doctors who have never treated Hodgkin know that there are two types, the classical, about 95%, and the nodular predominant Hodgkin lymphoma, the 5%. So, the pathology is very important. I was just in Dar es Salaam in Tanzania, and they asked me to give my recommendation for a Hodgkin patient. We did not know if it was Hodgkin or non-Hodgkin lymphoma and I asked them if they had immunohistology, and they said no we do not have that. It is important to have the CD30 and CD15 antibodies because these are the basic antibodies to recognize Hodgkin lymphoma, at least, the classical Hodgkin. Then, CD20 is in the nodular lymphocyte predominant Hodgkin, there it is more difficult to define if it is non-Hodgkin lymphoma or is it Hodgkin.

The second is the comprehensive knowledge about the instruments and modalities that are available today to diagnose and treat Hodgkin lymphoma. This means that we know that regular therapies may not be the mainstay anymore, and we should know that this is a very sensitive tumor that reacts extremely well to chemo and radiotherapy from the first. That means to treat according to the chance to cure this patient, according to the stage, and do not overtreat, because if you overtreat, the toxic effects will overwrite the effectiveness.

The third is to join forces to develop new and practical predictive markers for prognosis and response assessment. This might not account for the developing countries, but at least for the North American and European countries, and there we have to join forces in the molecular and molecular genetic sense.

Next is to join forces for global studies to better treat early and late stage Hodgkin lymphoma, especially to detect the lymphocytes predominant for pediatric and adult Hodgkin lymphoma. And, lastly, is increased awareness of the different cultural, ethnic, financial, political, special situations in the first-, second-, and third-world—here, I urge doctors not to exclude Africa—and the influence of the socioeconomic development. If they get more affluent, they get more Hodgkin lymphoma.

MHLC: *What you see are the biggest gaps between developing countries and developed countries when it comes to treating Hodgkin's?*

Dr. Volker Diehl: The biggest gap between the developing countries and developed countries is first the availability of competent doctors with knowledge of modern oncology and reliable health care systems. When I go to South America, Brazil, it is great in the big cities, but it is very poor out in the country. They have no oncologists, and they sometimes have no available drugs. Then the affordability to apply modern diagnosis and treatment strategies, this is very difficult in Russia, Ukraine, and in some Eastern European countries.

The next is reliable and competent pathology and immunohistology. If you do not diagnose Hodgkin as Hodgkin and have an aggressive non-Hodgkin lymphoma, you fail. If you have a Hodgkin and you have very clear diagnosis, you can treat it with ABVD or a little bit of radiation and you can cure the patient about 95%.

Another gap is awareness and education of standards of the general population in different countries and the compliance of the patients. If you have a young girl in Africa, you give her one ABVD or one BEACOPP, she goes home and she never comes back again, and you lose this patient. This means educate the population and try to get as much compliances as you can.

And then the question is, do they have available and suitable modern instruments or modalities and what are the alternatives to cure Hodgkin lymphoma? For instance, if you have brentuximab, it is so expensive that you pay about $30,000 in Buenos Aires and send the patient to Miami to get a shot of brentuximab. I have many patients down there who call me or write emails to me, and this is something where we might differentiate more and more rich and affluent countries from the poor developing countries with modern drugs that will be on the market, but they are very, very expensive.

Next is the lack of clinical trial organizations in developing countries. That means politics and even in the societies, the hematologic and oncology societies, they do not see the necessity to do clinical studies. Only by clinical studies do we learn more about the disease, about the outcome, and the toxicity of our drugs. The final gap is the lack of political, technical, and financial support to create a national standard for the care of Hodgkin lymphoma; that means missing guidelines, missing health care facilities like radiotherapy, PET, and the defined pathology with immunohistology. The government, the politics, and the caretakers have to sit together and build guidelines for diagnosis, for therapy, for follow-up, and education that is outreached to the population and to the patients.

MHLC: *You recently co-authored an expert opinion article on pharmacotherapy for Hodgkin standard approaches and a future perspective,*[3] *could you give us an overview of what the paper was about and what your conclusions were?*

Dr. Volker Diehl: This paper first summarizes the standard approaches. We, in Europe, differentiate between early intermediate or early unfavorable, early favorable, and advanced according to the EORTC Lymphoma Group criteria[4] and the German Hodgkin Study Group criteria[5]— the Americans and Canadians have only two stages, early and advanced. That means we have a very clear and gradual increase of intensity for the different stages and come up with about 90 to 95% in all stages with stage acquainted therapy: early two ABVD plus 20 Gray involved field radiation; intermediate four ABVD plus 30 Gray involved field radiation; and in the advanced stages, six ABVD or six escalated BEACOPP plus 30 Gray involved field radiation. This is the basic standard of our therapy with extremely high cure rates, more than 90%, and reduces toxicity by cutting down more and more of chemotherapy, and the dose and the fields of radiotherapy.

The second point of this paper was the future perspective, that means find sustainable and practical or predictive markers, molecular, immunological, and imaging, morphological, and metabolic markers and define more suitable staging criteria, possibly in the future even biologic, because not only Epstein-Barr virus (EBV) might be a

cause of Hodgkin's, but there seems to be another causal virus that is being pursued. So, it is possible in the future that there might even be vaccines, but this is a dream still.

And then define the role of the microenvironment in Hodgkin lymphoma. This is not only because we want to know why one person has mononucleosis and gets Hodgkin and the other one has mononucleosis or an EBV infection does not get it, and there, it is so important to understand the inter-talk between the Reed-Sternberg cells and the microenvironment. This reactive tissue that is attracted by the mediators produced and expressed by the Reed-Sternberg cells, and there comes then the role of the interacting factors, Hodgkin cell survival includes NF-kappaB JAK/STAT, PI3K/AKT, ERK, AP-1 notch and all these other receptor tyrosine kinases. These lead to the anti-apoptosis and proliferation of the Reed-Sternberg cells, but if we could break this interaction between these factors, the surrounding cells and the tumor cell, this would be excellent target for targeted therapy in the future.

Then we discussed different drugs that are in phase I, phase II, and phase III studies, and here, I think, that we should not only use those now in relapsing or refractory Hodgkin, since the longer we wait the more Reed-Sternberg cells and more aggressive cells we have because Reed-Sternberg cells, in my biological understanding, are very intelligent and genetically labile cells that increases in resistance and has a lot of secondary hits the longer you wait and more chemotherapy you give. Therefore, in North America and in Europe we have already started to use the new compounds, like brentuximab, in first-line treatment as well in early stages, intermediate, and in the advanced stages. This means we now have monoclonal antibodies, antibody direct conjugates, radioimmunoconjugates, bi-specific antibodies, and immunotoxins like brentuximab vedotin, lenalidomide, panobinostat, and everolimus.

Then, we describe the relapsed and refractory Hodgkin. It is high-dose therapy and autologous stem cell support for the first relapse, and then we give IGEF, DHAP, or ICE; and then if possible for the second, if we have it and can pay for it, brentuximab vedotin for the moment, but we cannot cure patients with brentuximab vedotin yet. Some patients have a very long-lasting complete remission, but we are not sure that we really can cure it with antiCD30 antibody. This was basically what we published in this paper.

MHLC: *There seems to be a global difference of opinion on ABVD versus BEACOPP for Hodgkin's lymphoma. Could you tell us what the main points of difference are?*

Dr. Volker Diehl: These different opinions are based on two different philosophies: the US-Canada-UK philosophy is you have two shots to cure HL—start mild and escalate—and the GHSG-European (GELA, EORTC) philosophy is you have only one shot, the

second is too weak. I think that we have only one shot because it is such a sensitive tumor cell, and if you kill the tumor cell there is 0.1 to 1% chance you would have a cure, and that means you have to treat hard at the beginning.

In America they think they have two shots, start mild and escalate late ABVD and then high-dose therapy and stem cell support. The first shot results in 70% complete remission and cure and the second shot gives 50% cure. That means you have 50% of the 30% failure which means 15, you come up to about, if you are lucky, to 85% total cure. There is a lot of toxicity with the second shot, AML, infertility 100% and so on.

The most important thing for me is if you ask the patient what they are most afraid of, getting a relapse or getting a second tumor? They are not concerned with infertility. They do not care about the toxicity if it is short and is quickly over. So, infertility comes at the fourth level. The first thing they say is, I do not want to get any relapse. So I think that we have only one real shot to cure Hodgkin lymphoma, and therefore, the European big study groups GELA, EORTC, German Hodgkin Study Group have their philosophy: You have only one shot. The second is too weak.

The fourth point is many countries do not have access to transplantation so they do not have the chance to get autologous bone marrow. If they use escalated BEACOPP, they have 95% overall survival without the high-dose therapy, and this is the reason why I think even if it is more toxic, definitely, it induces 80% to 90% infertility in young men, but I always say that does it help the young man if he is in heaven fertile. He wants to be here and we have frozen away his sperm and guess how many came back and asked for in vitro fertilization, less than 5% come back.

However, in young girls, it is extremely important. They will ask me, “Will I be able to have a baby?” And therefore, if we give six escalated BEACOPP, about 50% will not be able to have children, but many more woman are able to have children after 4 to 6 escalated BEACOPP. If you give 2 escalated BEACOPP, you will have about 80% fertility in girls and about 20 to 30% in young men, and we are just looking at this data from this clinical trial.

MHLC: *There are differing guidelines depending upon where a person is in the world. Do you believe that any particular set of guidelines should be adopted on a global scale, and if so, why?*

Dr. Volker Diehl: First, generally, global guidelines are difficult to establish due to the different basic needs, insufficiencies, and economical restrictions; that means, that some countries have no PET, no transplantation facilities, no availability of certain drugs, limited health care facilities, and few trained and competent oncologists. There is also

assumption, in some countries, that Hodgkin is often a luxury disease. But this is a bad situation and a completely wrong attitude toward this disease because it is the most curable adult cancer that we have besides testicular cancer.

Second, if you have global guidelines, then you should ask for minimal requirements. That means pathology with minimal immunohistology—CD30 and CD15—then you can try to differentiate between early, intermediate, and advanced stages. Because if you treat the early stages with six to eight ABVD, you have about 30% overtreatment. Therefore, we have early two ABVD, intermediate, four ABVD, and advanced six ABVD, or six escalated BEACOPP, you will cure most of the patients. Therefore, global standards and guidelines should take care of a good diagnosis, and then tailoring the therapy according to the stage. Unfortunately, we do not yet have the molecular markers, or the genetic, to decide from the beginning and predict the failure rate; we depend still on the old-fashioned grandfather anatomy and on the biological and chemical factors like we have in Germany, and the EORTC criteria to determine the treatment. And then, in countries where you do not have the facilities for autologous transplantation or even an allogeneic, then use six escalated BEACOPP plus 30 Gray involved field and you will come up to about 95% cure.

And the relapses, there we should write in the guidelines that nodal relapse needs radiotherapy and does not need high-dose therapy. Disseminated what we do in most countries: use two to four induction therapy, DHAP, IGEF, ICE, etc., and radiation if there are still nodal lesions left. You can then use brentuximab, some other generic—it would be fantastic if brentuximab gets cheaper—or other new agent in induction and in relapses.

MHLC: *The German Hodgkin study group recently released a comprehensive analysis on relapsed Hodgkin lymphoma in older patients. How do you think those results might help to guide treatment decisions and evaluate new compounds in these patients around the world?*

Dr. Volker Diehl: The older Hodgkin patients make up around 20% of Hodgkin patients. There increasing number of older patients because of demographic changes is important. We now experience more and more patients in a very good physical state, like being chronologically 60 or 70 but physically about 50 to 60. So, there is a change, and I think that the average situation in the age group will produce more Hodgkin patients because Hodgkin is an affluent society and only occurs in a certain immunological situation window. I think that older patients have a much better status than 10 or 20 years ago, so we might see much more adult-aged Hodgkin lymphoma.

But outcome is dependent on age, comorbidities, and the percent density of the primary therapy. If you have a patient over 60 years, they have comorbidities—cardiopulmonary and nephrological—and you plan to give them four to six ABVD but you have to stop after three because they can't tolerate it anymore. This means the completion of the first line therapy is prolonged over 14 days or three weeks, and even up to 4, 5, 6 weeks. Therefore, the outcomes are bad, not only with ABVD but with BEACOPP and all the other rational things we have used.

We have started a very interesting study, first in relapsed patients but now also as first-line for fit younger patients who need chemoradiotherapy. For older patients who need a series of more than 5 to 6 cycles, we tend to use brentuximab plus AVD, that means ABVD without bleomycin because of the pulmonary toxicity and lenalidomide, and with this we have less than 2% primary toxicity leading to death versus treatment-related mortality coming down from what it was with ABVD or BEACOPP.

MHLC: *You co-authored an opinion article on emerging drugs for Hodgkin lymphoma with Dr. Bastian von Tresckow,[2] who we have also interviewed for this series. Could you tell us about this article?*

Dr. Volker Diehl: My point in the article is that we have brentuximab vedotin now as a potential for the future treatment of Hodgkin, and it is an extremely important drug, but I do not feel it is a curing drug. It might be good in stage 1A. If you have very little tumor, you can give brentuximab and a little bit of radiotherapy if you still have a remaining lesion, but for more advanced disease, you need effective chemotherapy and in addition either brentuximab or the HDAC inhibitors, panobinostat, or mocetinostat and all these new drugs—like the mTOR inhibitor or the JAK2 inhibitor, SB1518, and the immunomodulatory agent lenalidomide—that are now in the pipeline. In phase I study, brentuximab gave 75% response and 37% complete remission.

All the other drugs that I mentioned now in the different interactions with the receptors or the pathways lead to about 15% to 35% response, some few complete remissions. So what we have to do in the future is define at what stage of the interaction between the tumor cell and the reactive cells we have to intervene, and try to break the communication between the tumor and the reactive cells. Possibly in the future, we might decide to use less toxic cocktails to act on different targets in the tumor cells and in the immunoreactive cells.

In the future, I think that we should focus on endeavors to find out how we can cure most Hodgkin patients without chemotherapy and radiotherapy, to look at the environment and inhibit the fostering task and function of the mothering cells, because without them the Hodgkin cell is a very fragile cell and will die. If you take it out from

the biopsy and you want to culture it, in 20 minutes it is dead, so it is a fragile cell, and we should concentrate on how we can inhibit this interaction between the mothering cell and the tumor cell.

MHLC: *What would you say is the biggest challenge on a global basis in the educational needs for doctors treating Hodgkin's?*

Dr. Volker Diehl: First of all teach the doctors the biology and the difference between non-Hodgkin lymphoma, leukemia, and Hodgkin lymphoma, and find out that they understand the molecular basis of the pathogenesis. Then for the practical daily use, make the right diagnosis of the pathology: how to diagnose Hodgkin lymphoma and differentiate from non-Hodgkin lymphoma entities.

Second is staging requirements, imaging, PET, laboratory, and then the German Hodgkin Study Group ERTC staging criteria for early, intermediate, and advanced Hodgkin as stage depends on treatment decision indicators. And the third is the response criteria catalog, everybody should know how to define a complete remission, partial remission, and a relapse; and what is short- and long-term toxicity analysis and prediction. So they should know when they give ABVD or BEACOPP what they have to expect in young and older patients. And the interventions in case of toxic side effects, as endocrine, pulmonary, cardiac, general, and psychological stress situations will come up, because we now find in Germany that we have more survivors that— after 10 or 20 years—go to private doctors for cardiac, pulmonary, endocrine problems, and the doctors have no idea about that. That means we have to teach the doctors and the patients what will come up after 10 or 15 years.

And, knowledge about new drugs and the agents. They should know that they are in the pipeline, the HDAC inhibitors and the brentuximab vedotin, the antiCD30 antibody. Give them information about ongoing clinical trails in Hodgkin lymphoma, locally, regional, nationwide, and global, because participation in the study is the best education for doctors who deal with patients. Today, the young patients come with the internet site of the Hodgkin or other study groups and say, "I want to participate in the study, because I think these are the best diagnosis therapy and follow-up."

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