Managing Hodgkin Lymphoma Expert Interview Series

An Update on Emerging Drugs for Hodgkin Lymphoma

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with
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Editor's Note:
Despite success in both treatment-naïve patients and patients with refractory or relapsed Hodgkin lymphoma (HL), new treatment options are needed. Novel treatments for HL will not only boost the response rates and durability of responses, but also decrease some of the toxicities seen using the current combined modality treatment regimens, which include secondary cancers and cardiovascular disease. There are a number of new treatment modalities currently being tested that are either in late-phase clinical trials or have recently been approved for use in the European Union (EU). On behalf of ManagingHodgkinLymphoma.com (MHLC), George Davatelis, PhD, spoke with Bastian von Tresckow, MD, medical head of the Clinical Trial Unit in the Department of Internal Medicine at Cologne University Hospital in Cologne, Germany, to discuss the robust pipeline of novel HL treatments and the current state of science in HL treatment in Europe.

MHLC: *Tell us a little about what you see as challenges in treating Hodgkin lymphoma.*

von Tresckow: Hodgkin lymphoma treatment is stage adapted because we want to avoid toxicity. We want to avoid long-term toxicity and acute toxicity, and in contrast to other cancers we have a very high cure rate in Hodgkin lymphoma. So especially in this disease, we have to balance the risks and the benefits of the therapies and to avoid unnecessary toxicities. I think this is the most important challenge, and I think the other challenge is that there are demographic changes and we have more and more older patients with Hodgkin lymphoma, and these patients have a quite poor outcome independently of what we use as first-line therapy. They do not tolerate BEACOPP (bleomycin, etoposide, Adriamycin, cyclophosphamide, Oncovin, procarbazine and prednisone), escalated, and with ABVD (Adriamycin, bleomycin, vinblastine and dacarbazine),[1] the outcome of patients in advanced stages is really poor, so we have to find new solutions for these patients. And the third thing is there is still dismal outcome

of patients with multiple relapses. At first relapse, we can only cure 50% of the patients. So for these patients, we also need new and better therapies.

MHLC: *How would you describe the standard of care for HL in Germany specifically, but also in the EU, and if you see any differences or similarities between how Germany works and how the rest of the EU works?*

von Tresckow: In the whole of Europe, we stage the therapy in Hodgkin lymphoma and generally we divide it into early stage, intermediate stage, and advanced stage disease. The standard is 2 cycles of ABVD followed by 20-Gy radiotherapy[2] for early stages. It is 2 cycles of BEACOPP escalated plus 2 cycles of ABVD plus 30-Gy involved-field for intermediate stages, and it is 6 cycles of BEACOPP escalated plus PET-adapted radiotherapy for advanced stages. There are slight differences in the use of BEACOPP escalated. This is especially true for the intermediate stages. I would say that 2 cycles of BEACOPP escalated plus 2 cycles of ABVD is not completely accepted in Europe as standard. A lot of centers prefer 4 cycles of ABVD, and even in Germany, depending on comorbidities of the patients, some prefer 4 cycles of ABVD for the intermediate stages. Besides not all centers do 6 cycles of BEACOPP escalated for advanced disease, a few also use ABVD which is standard of care in the US. However, most European cooperative groups use BEACOPP escalated for advanced Hodgkin lymphoma. For relapsed disease, we have a standard throughout Europe that is 2 cycles of DHAP (cytosine arabinoside, cisplatin and dexamethasone)[3] followed by high-dose chemotherapy and autologous stem cell transplant, depending on the risk factors of the patients, you can also do a tandem transplant.

MHLC: *There are many molecules right now that are in development, could you touch on some of the major categories or the ones you see as most promising?*

von Tresckow: Yes, I think on the one hand there is brentuximab vedotin in the class of antibody drug conjugates, and on the other hand, there are the small molecule inhibitors. In the latter group, there are HDAC inhibitors, mTOR inhibitors, and JAK inhibitors as well as lenalidomide.

MHLC: *In your opinion, do any of them look particularly promising?*

von Tresckow:I think it is quite evident that brentuximab vedotin is the most promising one. It has the best response rate in a large phase II trial.[4] There were 75% of patients responding, and one-third had complete remission. These are excellent results, and I think the other one which is really promising is the group of mTOR inhibitors. For example, there has been a trial with more than 60 patients, many with multiple relapsed

Hodgkin lymphoma, and there was a response rate of approximately 40% to everolimus monotherapy and the progression-free survival of 9 months in this trial. So, I think these two groups are the most important ones.

MHLC: Normally, when a new product comes on the market or is being tested, they are usually used in second line or as salvage therapy when everything else has failed. With the good data coming out on some of these new products, do you see any of them being pushed more toward first-line therapies?

von Tresckow: Definitely, and this is already being done. There has been a phase I trial with brentuximab vedotin and ABVD, and in first-line therapy, unfortunately there was a high rate of toxicity due to the combination of bleomycin and brentuximab vedotin.[5] That is why there is currently an ongoing phase III trial comparing AVD (ABVD without bleomycin) with brentuximab vedotin to ABVD standard therapy.[6] The other example is a German Hodgkin Study Group trial called targeted BEACOPP trial.[7] This is a first-line trial for advanced-stage Hodgkin lymphoma patient where BEACOPP escalated is detoxified by brentuximab vedotin. We have omitted the most toxic substances of BEACOPP escalated, and we have replaced it by brentuximab vedotin hoping that we will decrease toxicity while maintaining the high response rates which are, of course, higher than with ABVD, and the first result have been presented at last year's ASH (American Society of Hematology) and they look really promising.

MHLC: *How do you see the treatment paradigms evolving in the future?*

von Tresckow:I think treatment paradigms are not yet completely changing, but this is the first step. The long-term goal must be to replace the non-targeted chemotherapy and radiotherapy by new targeted substances. So, with brentuximab vedotin, we have the first targeted substance which might be used here, but we are not yet in the position to really replace radiotherapy or chemotherapy. But I think that in early stage disease, it might be considered to replace one of the modalities of first-line treatment.

MHLC: *How do you see some of these newer therapies working their way into the treatment paradigms for older patients?*

von Tresckow:I think these new drugs are particularly important for the old patients because they do not tolerate the aggressive treatments and especially in advanced stages they have a poor outcome with ABVD, so we need new approaches. And there are also ongoing trials with the combinations of new drugs and ABVD derivatives. For example, there has been the German Hodgkin Study Group AVD-Rev trial.[8] This was a trial combining AVD and lenalidomide, and as we had hoped, there was a good response

rate with this combination. It was a phase I trial, so we cannot compare those results yet to the standard of treatment, but it had a high efficacy. The overall response rate was about 80% and we think this is one example for an interesting regimen for the future. And moreover, there will be an international multicenter trial called B-CAP, and in this trial a CHOP-like regimen will be combined with brentuximab vedotin for older patients.

MHLC: *What do you see has the greatest potential to impact and improve outcomes specifically in Germany but also in the rest of the EU?*

von Tresckow:I think currently it is brentuximab vedotin because for 30 years we had no new therapy for Hodgkin lymphoma. It is the first step right now that we have toward the targeted therapy, and this is the first drug which is really used to replace non-targeted compounds of the combined modality treatment. In the last 30 years, we only had these non-targeted therapies, so we are of course happy and excited that we now have something new to combine with the established therapy.

MHLC: *What are the key educational needs that you see for clinicians in both Germany and the rest of the EU?*

von Tresckow:I think for clinicians, it is very important to understand the paradigms of stage-adapted therapy and really tailor the therapy as far as possible right now via using this three-stage model with early stage, intermediate stage, and advanced stage patients. This is to avoid unnecessary toxicity but to still cure most patients of this disease. The other thing is that we know that most therapies are non-targeted and toxic, and we have to take care of the side effects, both during and also after therapy. We have to take measures to preserve fertility before the start of therapies in young men and women, and we have to take care of the toxicity surveillance after therapy. That means we have to take care for cancer prevention measures and to carefully follow up the patients. So there is already a decrease of secondary cancers after Hodgkin lymphoma, but I think our goal must be to further decrease secondary cancers, and the new drugs, of course, gives us opportunities to do that.

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