Managing Hodgkin Lymphoma Expert Interview Series

CD30+ Hematological Malignancies: Current State of the Science

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with
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Editor's Note:
Hodgkin lymphoma (HL) is a relatively uncommon hematologic malignancy with an annual incidence of approximately 2-3 people per 100,000 in the European Union (EU) and the United Kingdom.[1] Standard treatment of adults with HL consists of classical chemotherapy with either ABVD (Adriamycin [doxorubicin], bleomycin, vinblastine, and dacarbazine) or BEACOPP (bleomycin, etoposide, Adriamycin, cyclophosphamide, Oncovin [vincristine], procarbazine and prednisone) and is often followed by radiotherapy in a combined modality setting.[2] The treatment of patients with HL is one of the major success stories in oncology and 60% to 90% of patients—depending on clinical stage and risk factors—are cured of their malignancy.[3] However, current combined modality treatment regimens for first diagnosed HL patients can induce severe, life-threatening treatment-related side effects, including secondary cancers and cardiovascular disease. 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 approximately 50% of patients.[2] Despite success in both treatment-naïve patients and patients with refractory or relapsed disease, new treatment options are needed. One such new approach is to focus on the expression of the CD30 antigen, a cell surface receptor that is abundantly expressed on the cells of several hematological malignancies, including malignant Hodgkin-Reed Sternberg (HRS) cells and anaplastic large cell lymphomas.[4] On behalf of *ManagingHodgkinLymphoma.com* (MHLC), George Davatelis, PhD, spoke with Tim Illidge, BSc, PhD, professor of targeted therapy and oncology at the School of Cancer and Imaging Sciences of the University of Manchester, to discuss the latest advances and current state of science in Hodgkin lymphoma treatment and other CD30+ hematological malignancies.

MHLC: *What is the state of care in Hodgkin lymphoma in the EU?*

Dr. Tim Illidge: Well, I do not think there are significant differences between clinical practices in the EU and the United States. Two of the areas of current controversy are the use of fluorodeoxyglucose-positron emission tomography (FDG-PET) scanning to influence treatment decisions and the second broad area is the use of BEACOPP versus ABVD for initial therapy. As regards to PET, it is increasingly been used as an imaging biomarker in making treatment decisions regarding whether patients should have an escalation in treatment if they are PET positive or de-escalation in treatment if the PET scan is negative. This decision can involve the removal of radiotherapy if PET negative. Most of the controversies are in the interpretation of the emerging data in those areas and the accessibility of FDG-PET imaging to be able to make those decisions between US and EU. In Europe, BEACOPP is used more often, especially by the German Hodgkin Study Group, than in the US.

MHLC: *Can you address the pros and cons of using BEACOPP versus ABVD?*

Dr. Tim Illidge: I think most lymphoma specialists would acknowledge that BEACOPP is a more efficient treatment than ABVD, although that still is a controversial statement as no randomized trial has demonstrated an overall survival advantage for BEACOPP over ABVD. The major question appears to be around who requires BEACOPP to be cured because we know that around 80% of patients will be cured with ABVD as a standard of care. So, many would consider that the benefits for BEACOPP in whatever form that is given, escalated BEACOPP or the standard BEACOPP, are relatively marginal in so much if we know that 70%-80% of patients will be treated unnecessarily with a more toxic treatment, including the loss of fertility to get to the same point. So, the optimal approach remains a controversy, and therefore we are trying to address using FDG-PET directed clinical studies across the world with the key question, “Can we select a population of patients based on FDG-PET that require escalation to BEACOPP therapy after initial ABVD therapy?” And over the next 2 to 3 years, data will emerge which will inform that discussion.

MHLC: *Do you follow any specific guidelines, and if so, which ones are they?*

Dr. Tim Illidge: We have the British Society of Hematology Standard Committee,[5] and they have a group which meets together on an annual basis to consider the evidence and publish them with national guidelines, and they are usually published within the *British Journal of Hematology*, and those guidelines will go out to peer review. I find

them to be thorough and having gone through a robust process, and that is usually what we go with within the UK.

MHLC: *The topic of this interview is the current state of science with CD30-positive hematologic malignancies. Can you first tell us exactly what CD30 is?*

Dr. Tim Illidge: CD30 is an antigen which is present on a number of activated T-cells. It has no expression or a much lower level of expression on normal tissues. The story really goes back more than 30 years when this particular antigen was discovered on the surface of Hodgkin Reed-Sternberg cells by Harold Stein and his group in Cologne,[6] who generated an antibody Ki-1 which recognized an antigen on a patient-derived Hodgkin lymphoma cell line. We subsequently know this antigen as CD30, and the CD30 antigen is a defining feature of anaplastic large cell lymphoma and Hodgkin Reed-Sternberg cells, and it is part of the super family of tumor necrosis factor receptors. It is an extremely good target in lymphoid malignancy because of the differential expression that it has on a range of T- and B-cell lymphoid malignancies in addition to Hodgkin lymphoma and anaplastic large cell lymphoma. We are increasingly finding that it is present on some normal tissues and, more recently, low levels of CD30 expressions have been found in the pancreas, and we know that it also is present in the lungs, so it is not an absolute tumor-defined antigen but has a very preferable level of expression on tumors relative to normal tissues.

MHLC: *Adcetris (brentuximab vedotin) is an antibody-drug conjugate (ADC) directed to the protein CD30, and it was recently approved in both the US and EU for refractory HL. Can you describe this drug for us?*

Dr. Tim Illidge: Yes. Brentuximab vedotin is the first of its class antibody-drug conjugates that combines an anti-CD30 antibody with a potent drug of monomethyl auristatin E (MMAE) through a proteolytic cleavage site so that the drug remains on the antibody as it is targeted to the CD30.[7] The CD30 antibody-drug conjugate is bound initially to the antigen on the tumor cell. The antibody-drug conjugate is then internalized with the CD30, the complex is broken down, and the linker between the drug and the antibody is cleaved through proteolytic cleavage site and the drug is released internally in the cytoplasm. The drug itself kills the tumor cells. It is understood to do this through apoptosis, but it is almost certain that the drug leaks out of the dying cell into the surrounding tumor microenvironment which is the reason why we might observe death of the surrounding tumor cells, and probably also explains why it is so effective in Hodgkin lymphoma and also why we might see some of the non-specific off-target side effects such as the neuropathy.

MHLC: *How effective is Adcetris in combating recurrent HL?*

Dr. Tim Illidge: The overall and complete response rates are really very impressive indeed with an overall response rate of 75% and a complete remission rate of 34% of patients. The median progression-free survival time for all patients was 5.6 months, and the median duration of response for those who achieved a CR was 20.5 months. The pivotal registration study was done in a group of patients post-salvage high-dose chemotherapy and autologous stem cell transplant where the expectation for this group of patients is really usually pretty poor, and in particular, if you relapse within 6 months of an autologous stem cell transplant, usually your survival is somewhere between 6 and 12 months. So, these initial durable response rates were encouraging, with more than a third of these relapsed and refractory patients achieving complete response rates. Perhaps even more impressive now is that with longer-term follow up, some durable remissions are being seen with drug alone. It is clear that some of these patients who traditionally, looking at historical controls, would have had a median survival of between 6 and 12 months. There is clearly a group of patients that appeared to have gone into long-term remission, albeit that group of patient is relatively small.

MHLC: *This drug has been approved for refractory disease or after autologous stem cell transplant, but there are some who say that it might be beneficial in earlier stages. What is your opinion on that?*

Dr. Tim Illidge: Well, given the activity of the single agent in relapsed post-transplantation, it is a really important question to address. This is being done so in a robust fashion through a large international effort with a randomized phase III study. The initial phase II data which does have the phase III study are provocative into much of, they told us, two things. The first point to emerge was that it was not possible to add the drug brentuximab vedotin to the standard ABVD, as the bleomycin interacted and appeared to increase lung toxicity. So, the ECHELON-1 study is essentially a phase 3 randomized, two-arm trial of brentuximab vedotin plus AVD (doxorubicin, vinblastine, and dacarbazine) versus ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) as front-line therapy in patients with advanced classical Hodgkin lymphoma. We expect to know the answer to this important question within the next 5 years. The ECHELON-2 study, which is equally important, compares peripheral T-cell lymphomas and CD30-positive mature T-cell lymphomas, NK/T-cell lymphomas, as well as anaplastic large cell lymphoma. The study compares CHOP, which is somewhat unspectacular standard of care, versus CHOP (cyclophosphamide, hydroxy doxorubicin, vincristine [Oncovin], prednisone) without the vincristine with brentuximab vedotin in a randomized fashion. My speculation is that both of these trials have a good chance of improving the outcome

for patients, and I would be hopeful given the compiling phase II data that they would show a benefit over current standard of care.

MHLC: *Finally, what does the future hold for regarding CD30-positive malignancies?*

Dr. Tim Illidge: Well, I think there is an evolving area that we talked about earlier. An important question which we currently do not know the answer to is what is the level of CD30 expression that is required to get a good clinical response to the drug? So, at the moment, we are strongly advising hematologists and expert lymphoma pathologists to ask the question, "Does the tumor express the CD30 antigen?" And that is a very important message to develop. Only if we address this as a larger community will we be able address the question of the level of expression that is required to make it a clinically meaningful response to the patient. Furthermore, another difficult discussion within our health economies is the issue of cost-effectiveness. This data which will emerge over the next few years will inform the debate and give us a better understanding of what is the best way to measure CD30 expression levels. We need to develop the appropriate biomarkers to know which patients are going to benefit so we can not only pick the right drug for the right patients but, importantly in the age of targeted therapy is that they are becoming increasingly expensive, make it as cost effective as possible for the health care providers.

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