Managing Hodgkin Lymphoma Expert Interview Series

An Update on the Current State of Hodgkin Lymphoma Care in Japan

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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 Dr. Michinori Ogura from the Department of Internal Medicine and Laboratory Medicine, National Hospital Organization Suzuka National Hospital, Suzuka, Japan, to discuss the latest advances and current state of HL treatment in Asia.

MHLC: *Compared with the West, Hodgkin lymphoma in Eastern Asian countries is characterized by a lower incidence rate and a higher proportion of mixed cellularity histology. Can you tell us a little about this and what the standard of care for HL is in Japan?*

Dr. Ogura: Until now, there are 3 multicenter prospective clinical studies of Hodgkin lymphoma conducted by the Lymphoma Study Group of Japan Clinical Oncology Group (JCOG) in Japan. In JCOG9305 study, a phase II study of ABVd with the lower dose of dacarbazine (250 mg/m^2) in patients with newly diagnosed Hodgkin lymphoma with stage II, III or IV, % of NS and MC was 69.6% and 22.5%, respectively.[3] In JCOG9705 study, a phase II study of ABV with an increased doxorubicin dose (30 mg/m^2) in newly diagnosed advanced stage Hodgkin lymphoma, % of NS and MC was 58.6% and 15.7%,

respectively.[4] In an article of HD10 and HD11 studies from Germany in JCO in 2013, % of NS and MC was 59% and 27%, respectively.[5] So, I think there is no different about the proportion of subtypes in Hodgkin lymphoma.

In Japan, a standard care for HL is ABVD. In early stage with good risk HL, 2 cycles of ABVD followed by 20Gy IFRT is a standard of care. In early stage with poor risk HL, 4 cycles of ABVD followed by 30 Gy IFRT is a standard of care. In advanced stage HL, a standard of care is response oriented ABVD (if CR is obtained after 4 cycles, additional 2 cycles will be delivered, and CR will be re-confirmed after 6 cycles, no more therapy will be delivered. If PR or SD is obtained after 4 cycles, additional 2 cycles will be delivered, and CR will be obtained after 6 cycles, 2 more additional cycles will be delivered (a total of 8 cycles). If CR is not obtained after 6 cycles, salvage therapy is indicated.

MHLC: *What are the treatment challenges in treating HL in Japan and how do you think they differ from other areas in the world, say the EU or the US?*

Dr. Ogura: How to judge the patients who will be poor responders to ABVD is a big challenge. In Japan, we at the JCOG Lymphoma Study Group are preparing to start a phase II study of PET guided treatment in newly diagnosed advanced stage HL. In PET-negative patients after 2 cycles of ABVD, additional 4 cycles will be delivered, and in PET-positive patients after 2 cycles of ABVD, dose escalated 6 cycles of BEACOPP will be delivered. In Japan, there is very little experience of dose escalated BEACOPP, so we will evaluate the safety of dose escalated BEACOPP in this JCOG study. The delay of this type of study is a difference between Japan and the US and Europe.

The optimal treatment in primary refractory HL or relapsed HL without eligibility for auto-PBSCT or relapsed HL after auto-PBSCT is another big challenge. Recently, brentuximab vedotin was approved for relapsed or refractory HL in Japan. So, optimal use of brentuximab vedotin is also a big challenge.

MHLC: *We know that all new drugs coming into Japan need to go through a Japanese PK/PD clinical trial to get approval. Even so, do you think that Western HL clinical trial results, both European and the US, are relevant to Asian clinical practice?*

Dr. Ogura: Generally, I think that Western HL clinical trial results, both European and the US, are relevant to Asian clinical practice. However, toxicity profile especially in molecular targeted drugs is rarely different between Japanese and Caucasian. So, I think that the regulation of PK/PD test of new drugs in Japan is unavoidable.

MHLC: *Since over 80% of HL patients are cured using SOC, treatment-related side effects seems to become a major issue. Can you tell us what the latest thinking is in Japan to address such concerns?*

Dr. Ogura: As you know, toxicity of chemotherapy in HL includes acute and late toxicity. For acute toxicity, current thinking in Japan is about the use of G-CSF in ABVD. In the US and Europe, routine prophylactic use of G-CSF is avoided because of negative impact to efficacy. Some physicians in Japan use G-CSF in ABVD to maintain 14-days interval. I agree with guideline in the US and Europe. Pulmonary toxicity by bleomycin is another important AE in ABVD. In JCOG study, all patients were monitored for PaO2 just before ABVD administration, and no severe toxicity was observed until now. In clinical practice, we recommend physicians monitor SaO2 routinely just before the administration of bleomycin.

For late toxicity, infertility is one of the concerns. However, as you know, infertility is rare in ABVD. However, we must take much more care for BEACOPP or salvage therapy. Second malignancy is another serious late toxicity in HL treatment. Although second malignancy is rare in ABVD, careful monitoring is essential especially in salvage chemotherapy including auto-PBSCT and BEACOPP. We also must take care for other late toxicities including cardiac and pulmonary toxicities especially in patients who had irradiation therapy. For brentuximab vedotin, hematologists in clinical practice should learn about the efficacy and toxicity of this new drug, because this new agent launched only 5 months before in Japan.

MHLC: *I noticed that you wrote a paper on new drugs in development for lymphomas in Japan. With so many new types of drugs being tested for Hodgkin's, (antibody drug conjugates, HDAC inhibitors, mTOR inhibitors, JAK inhibitors, etc.), do any of them look particularly promising in your view?*

Dr. Ogura: In Japan, only brentuximab vedotin was developed in HL. No other drugs including HDAC inhibitors, mTOR inhibitors or JAK inhibitors were developed for HL in Japan until now. I believe brentuximab vedotin is the most promising agent for HL in new drugs recently developed in the world.

MHLC: We know that you and your team recently published a paper on a phase I⁄II study of brentuximab vedotin in Japanese patients with relapsed or refractory CD30-positive Hodgkin's lymphoma or systemic anaplastic large-cell lymphoma.[6] Can you summarize that trial and any data you may have accumulated?

Dr. Ogura: To assess its safety, pharmacokinetics, and efficacy in Japanese patients with refractory or relapsed CD30-positive HL or systemic anaplastic large-cell lymphoma

(sALCL), we carried out a phase I/II study. Brentuximab vedotin was given IV on day 1 of each 21-day cycle up to 16 cycles. In the phase I part of a dose-escalation design, three patients per cohort were treated at doses of 1.2 and 1.8 mg/kg. In the phase II part, a dose of 1.8 mg/kg was given to 14 patients (nine with HL and five with sALCL). The median number of treatment cycles was 16 (range, 4-16).

In the phase I part, no dose-limiting toxicity event was observed. In the total population, common adverse events included lymphopenia (80%), neutropenia (65%), leukopenia (65%), and peripheral sensory neuropathy (60%). Grade 3/4 adverse events in more than two patients were lymphopenia (50%) and neutropenia (15%). The PK profile was similar to that observed in the previous studies in the USA. In the phase II part, six patients (67%) with HL achieved an objective response with 56% of complete response rate, and five patients (100%) with sALCL achieved an objective response with 80% of complete response rate. These results show that brentuximab vedotin has an acceptable safety profile and promising antitumor activity in the Japanese population. Relative number of patients who achieved CR relapsed after the final 16th cycle of brentuximab vedotin. So, another treatment after brentuximab vedotin, or combined therapy with brentuximab and another drugs or sequential therapy of brentuximab vedotin followed by chemotherapy, or optimal maintenance therapy of brentuximab vedotin should be developed.

MHLC: *Demographic changes are resulting in a higher number of older patients being diagnosed with HL in the coming years. With this changing demographic, how should physicians treat elderly patients with Hodgkin lymphoma both in Japan and the rest of East Asia?*

Dr. Ogura: In Japan, there is no evidence-based standard of care in older patients, especially aged 75 or 80 years or more. In elderly patients with good PS and no comorbidity, ABVD is considered as a standard of care and utilized. For older patients with early stage HL, 2 cycles of ABVD followed by 20Gy IFRT is recommended. For advanced stage HL, 6 or 8 cycles of ABVD is also indicated for older patients. For elderly patients, bleomycin might be omitted especially in patients with preexisting pulmonary comorbidity. Dose intensity of ABVD is decreased under a critical limit of 65% in older patients. So, brentuximab vedotin with short cycles of AVD or brentuximab vedotin with dose-decreased AVD should be evaluated in older patients with HL.

MHLC: *What do you think are the key educational needs of the clinicians in your country and the rest of Asia?*

Dr. Ogura: We need to better educate the epidemiology and diagnosis of HL. In addition, I believe we need to educate what is the standard of care in newly diagnosed and relapsed HL based on the important key clinical trials. Finally, we need to educate physicians on the toxicity profile in key chemotherapy and key drugs in HL.

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