Managing Hodgkin Lymphoma Expert Interview Series

A Global Perspective on the Current State of Hodgkin Lymphoma Care

George Davatelis, PhD – Moderator/Writer
with
Massimo Federico, MD
Director, Medical Oncology Unit
University of Modena and Reggio Emilia
President, Italian Lymphoma Foundation
Modena, Italy

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 Massimo Federico, MD, director of the Medical Oncology and Lymphoma Unit at the University of Modena and Reggio Emilia, and president of the Fondazione Italiana Linfomi (FIL), to get a global perspective on the latest advances and current state of science in HL treatment.

MHLC: *What do you think are some of the shared needs for Hodgkin lymphoma among different regions of the world?*

Dr. Massimo Federico: To be honest, the only difference we observe in terms of treatment opportunities, and of course in terms of potential of cure, is dependent on the availability of the most effective treatment strategies. So in the rich countries, on the average in the Western countries and in the rich Asian countries, there is no difference either in terms of treatment strategies or in terms of differences in needs. Of course in less developed countries, or in disadvantaged countries, there are several differences because they cannot start with current treatments and then they need to rely on the traditional, and unfortunately less effective treatment. Thus, I believe that the difference is just in terms of financial support for the general population.

MHLC: *You recently co-authored a paper which is an epidemiological overview of Hodgkin's across the entire Mediterranean Basins.*[3] *Please give us a brief overview of your findings, and more importantly, tell us if you think that your findings could be extrapolated to the rest of the world.*

Dr. Massimo Federico: First, it emerged from our current investigation that there is a substantial variation in HL occurrence by geographic area: HL incidence rates progressively decreased from industrialized European countries such as France and Italy to less developed nations such as Albania and Bosnia Herzegovina, confirming the positive correlation between degree of socio-economic development and risk of HL. The remarkable differences in the global occurrence of HL, with incidence rates higher in Southern Europe than in Northern Africa and Western Asia, seem to be largely due to a higher exposure to risk factors associated with Westernization, as well as availability of diagnostic practices and awareness of disease. And it seems, very surprising, that in a very limited area—that means the Mediterranean Basins where there are less than 300 miles from Italy to Libya, for example, or from Italy to Giordania—there is so a huge difference in the epidemiology of the disease. Of note, in the Arabic populations the incidence is very low compared to the other countries in the same area. So, I would expect that the low incidence rate we observed in Northern Africa would be also expected for people living in the Arabian Peninsula. I visited Saudi Arabia last week and had the opportunity to talk in a meeting on Hodgkin lymphoma, and their epidemiology is similar to what we observed in Libya, and so the incidence is lower.

MHLC: *Regarding epidemiology, there is a study that showed that Chinese emigrants, who have a low endogenous rate, began to show the same rates of Hodgkin's as Westerners when they immigrated to Canada. Can you help explain this?*

Dr. Massimo Federico: This means that environmental influence must also be taken into account. So, the difference in the incidence is mostly dependent on the environment that we have, and its effect on the immune system.

MHLC: *There are different guidelines in the world. Do you believe that any particular study guidelines should be adopted on a global basis?*

Dr. Massimo Federico: Once again, the difference is how rich is the population or how rich is the country. So, the guidelines we developed in Europe or have been developed in the US are very similar, very few differences. And then, we can alternatively apply the European guidelines for US population or the American guidelines for the European population, but probably, it is difficult to apply the same guidelines in poor countries. To some extent also in South America, it is not easy to guarantee the same opportunities. For example, the recently published new guidelines for staging, response assessment, and follow-up of patients with lymphoma (the Lugano classification)[4] allow to avoid

bone marrow biopsy if you use PET scan for staging. It is most likely that this approach will be adopted in rich countries. But if in poor countries, PET facilities are not available of course thus you have to use different guidelines both in terms of staging and in terms of initial treatment. So, guidelines that are available for Europe and US are very similar and could be also exported in countries with the same level of opportunities. I imagine that probably could be exported to Israel or Japan or South Korea, or of course to Australia and New Zealand, but it is difficult to export the same guidelines to Madagascar or Ciad.

MHLC: *I wanted to ask you about some of the key issues concerning the treatment of patients in early stage. What is your standard of care for Hodgkin's for these patients?*

Dr. Massimo Federico: In Italy we have two different approaches depending on the extension of early stage because we have different guidelines for early favorable and early unfavorable HL. For the first one, early favorable, we propose 2 or 3 courses of combination of chemotherapy with ABVD plus involved site radiotherapy. For early unfavorable, the standard is 4 or 6 courses of ABVD again followed by involved site radiotherapy.

The German Hodgkin study group also developed guidelines for treating patients with HL. They have the same approach we have for early favorable, but for early unfavorable they prefer to start with 2 courses of BEACOPP escalated followed by 2 courses of ABVD and then, if indicated, the radiotherapy. So, this is currently the standard of care for early Hodgkin lymphoma, and this information has been also summarized a few weeks ago with the release of the European guidelines for treatment of Hodgkin lymphoma released by the European Society of Medical Oncology.[5] Probably in the near future, we will adapt to this paradigm also using PET for response assessment, and then probably we can reduce the number of courses of chemo, or in some cases, we hope to again avoid the necessity of radiotherapy. But to change the standard of care, we need at least a couple of years to know the final results of the ongoing or recently concluded large randomized trials.

MHLC: *What would be your standard of care for advanced-stage Hodgkin?*

Dr. Massimo Federico: In my opinion ABVD should still be considered as the standard outside of clinical trial. However, for the German Hodgkin Study Group, BEACOPP escalated should be the standard. At present, I offer 6 to 8 courses of ABVD to patients with advanced-stage disease; probably in the near future, we can have a different approach once the results of the response-oriented trials that have been recently concluded or that are being concluded now will be available. So for the future, probably, the treatment would be driven by PET response after 1 or 2 courses of chemotherapy. For those patients who respond well to ABVD—probably 75-80% of patients with

advanced-stage Hodgkin lymphoma— ABVD should continue to be the standard, and probably, there is also room to eliminate bleomycin from the last courses. For those patients who do not respond well to the first 1 or 2 courses of ABVD, then it is probably realistic to shift to BEACOPP escalated. This is my preferred approach.

MHLC: *Could you tell us your opinion of brentuximab vedotin?*

Dr. Massimo Federico: Brentuximab vedotin has represented a major advance in the treatment of Hodgkin lymphoma, showing the highest single-agent activity ever registered within a subset of heavily pre-treated patients. This excellent results accelerated the approval of the drug for the refractory/relapsed setting and, at the same time, facilitated its investigation as a component of first-line regimens. According to FDA and EMA, brentuximab vedotin is now indicated for the treatment of patients with HL after failure of autologous stem cell transplantation or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates. Evidence is now strong for recommending brentuximab vedotin also in patients who are ASCT candidates. At present, a large phase III trial (ClinicalTrial.gov, number NCT01712490) is ongoing, investigating the efficacy of brentuximab vedotin plus AVD compared to standard ABVD in newly diagnosed HL patients. We had also the opportunity to test brentuximab in first-line therapy, in patients with early Hodgkin lymphoma. We started with 2 courses of brentuximab alone, and then we moved to standard therapy with ABVD and radiotherapy. After 2 courses of brentuximab we observed a complete metabolic response in 10 patients, that means 83%, and one additional patient had a partial metabolic response. So, the overall response rate was 92% before starting with ABVD. In this study all patients but one started ABVD in the absence of signs of Hodgkin lymphoma. Based on these impressive results, I believe that brentuximab should be tested as single agent in patients with early Hodgkin lymphoma, possibly avoiding the toxicity of additional chemotherapy and radiotherapy. For advanced-stage, the ongoing trial that is now being conducted in Europe, US and other countries will probably determine if the addition of brentuximab in the place of bleomycin in the ABVD regimen will determine more complete responses, and benefit in terms of prolonged PFS and eventually overall survival, thus emerging as the new standard, although more expensive than 6 courses of ABVD.

MHLC: *Yes, especially in elderly patients. With the toxicity levels coming down, even that would be a good trade-off, I would think.*

Dr. Massimo Federico: Probably in elderly patients it is reasonable to offer brentuximab alone and add some chemo only if necessary, in a subsequent phase. Of course we need the more mature data for that. But, this could be a reasonable perspective, at least for some patients.

MHLC: *There are some big challenges around the globe in managing Hodgkin, and if you could change one thing in different countries around the world, how would you fix the challenges that you see?*

Dr. Massimo Federico: Hodgkin lymphoma is unquestionably considered one of the most successful stories of modern oncology. However the excellent outcome of this cancer must not make us forget those critical issues still pending. In particular, the young age of most patients as well as the proportion of them failing to achieve durable remission with first-line therapy requires to continue adequate research in the field and the introduction of novel targeted therapies may represent an additional opportunity to improve disease control while reducing the risk of long-term consequences. My hope and desire is to have the opportunity to offer the best available therapies to all patients with Hodgkin lymphoma, irrespective of the country where they live.

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