Frontline Updates From the Annual Hematology Meeting: Advances in the Treatment of Lymphoma
DR. WILLIAM MENCIA: Hello and welcome to Med-IQ’s coverage of the 2013 American Society of Hematology Annual Meeting. I’m joined today by Dr. Luciano Costa, Associate Professor of Medicine at the Medical University of South Carolina. Welcome Luciano.

DR. LUCIANO COSTA: Thanks for having me.

DR. MENCIA: We’re hearing a lot of data on new agents in the area of lymphoma at this conference. What can you tell us about that?

DR. COSTA: There are a lot of exciting new agents. I think over the past year or two there was a lot of attention paid to tyrosine kinase inhibitors. I think at this meeting the highlight is really on the PI3 kinase inhibitors. Other agents that we also saw a lot of new very exciting data on are the monoclonal antibodies, both novel CD antibodies, but also we saw a lot of interesting data on B vedotin (brentuximab vedotin) being used in histologies or conditions other than relapsed Hodgkin and anaplastic large cell lymphoma. Another interesting group of data we saw was not only on novel agents but perhaps different uses for prior agents. We’re seeing a lot of data on lenalidomide being used in earlier phases, earlier in the natural history of the disease, particularly in indolent lymphoma and in combination with chemoimmunotherapy.

DR. MENCIA: There is certainly a lot to talk about in this area. Let’s start breaking this down and looking at some of the individual therapeutic targets. Let’s start with the PI3 kinase inhibitors.

DR. COSTA: There’s essentially one thing that all those agents share in common—they target the delta isoform of the class I PI3 kinases. We have agents that are more selective, like idelalisib, which seems to be a little more ahead in terms of drug development. We have other agents that are multi-isoform, for example SAR245409. We also saw in this meeting data on BAY 80-6946, which aims particularly at the alpha and delta isoforms. I think the key question on the PI3 kinase inhibitors is, are you better off with a more...
specific and potent delta PI3 kinase isoform inhibitor or are you better off with broader PI3 kinase inhibitors that also affect other isoforms.

The data we’re seeing emerging at this meeting and before make it very hard, and I think it would be extremely premature, to try and compare across agents. The populations in the trials are very different. For example, the phase 2 multi-histology trial with idelalisib had a relatively large population—I think over 100 patients across all of the end-line histologies. We saw very, very high activity, particularly in small lymphocytic lymphoma, but perhaps a little bit less so in follicular lymphoma and mantle cell lymphoma. It had a very good safety profile, essentially limited to some GI toxicity and to some kind of interspecific low-incidence, low-grade toxicity. We also saw data on SAR245409, which were really limited to follicular lymphoma even though the data came from a larger trial with several arms. The display at the meeting was limited to follicular lymphoma, where we saw about 40% activity.

Also interesting was another trial, with BAY 80-6946, which is a bigger compound and was presented by a German group. What we saw was even broader eligibility. This is a trial that had patients with indolent lymphoma and with aggressive lymphoma, including large cell lymphoma but also T-cell lymphoma. What I think was interesting were the responses and tolerability in the indolent lymphomas—in the same ballpark as with the other agents—but also the activity in T-cell lymphoma. I think the difference we’re seeing now has more to do with trial design eligibility than with differences between the agents.

DR. MENCIA: There are certainly a lot of interesting data to look forward to in this area.

DR. COSTA: Absolutely.

DR. MENCIA: Let’s turn our attention now to brentuximab. We’re hearing some information about its use in clinical trials. What can you tell us about brentuximab?

DR. COSTA: Brentuximab has been around for a couple of years now, essentially as a treatment for relapsed Hodgkin’s
lymphoma after autologous transplant if the patients are not eligible for an autologous transplant or for relapse in anaplastic large cell lymphoma. First and foremost, this trial had a longer follow-up than the pivotal trial that led to the approval for Hodgkin’s lymphoma—now approaching 3 years—which I think is very important because this tells us not only the response rate, which was the initial finding and didn’t change (about 75%), but it also gives us an idea of the durability of the response and of how that really impacts survival and future treatment choices. With about 3 years of follow-up, they reported a median overall survival of 40 months; to put this into perspective, the historical control on that situation is about 2.5 years. There is clearly an unmet medical need.

This trial involved single-agent B vedotin initiated in patients over the age of 60. They were considered by the investigator to not be eligible for conventional treatments. Only very early data are available. This was a poster reporting on, if I’m not mistaken, about 12 patients with a median age of 75—so the data captured very old patients with Hodgkin lymphoma. We saw responses in essentially all but two patients. Again, it’s too early and the numbers were too small to determine the exact response rate, but it’s really exciting to see such responses for an agent that is well tolerated. You had the usual cases of neutropenia and some peripheral neuropathy, but nothing compared to what you’d expect when you give multi-agent chemotherapy to a population of this age.

Another very interesting thing that was presented at the meeting was a study from the group at MD Anderson, which essentially looked at cutaneous T-cell lymphomas. I think for most oncologists, and even for some lymphoma doctors, this is a bit of an obscure group of diseases, because they have a low frequency and can have very diverse histologies. This trial included classically CD30-positive lymphoid papulosis and cutaneous and anaplastic T-cell lymphomas, but also included a subgroup of patients who had mycosis fungoides, which is the most common of those cutaneous T-cell lymphoma histologies that happen to be CD30-positive.

Again, there were small numbers, so it’s hard to make too much out of it. But, essentially, it was not surprising...
that there was a 100% response for lymphomatoid papulosis and T-cell lymphoma. But, perhaps the more interesting finding was that the mucosa from about 50% of these patients showed an objective response to B vedotin. We also saw very interesting data in other more common histologies and in B-cell lymphomas. B vedotin has been associated with Hodgkin’s and anaplastic T-cell lymphomas. But a subgroup of patients with, for example, large cell lymphomas also expresses CD30, which makes it an obvious target for B vedotin. In a population of mostly patients with relapsed refractory disease, a very tough population if you’re dealing with aggressive lymphoma, you’ve got a response rate of about 40%. This, again, is very exciting and that’s a group of patients who desperately needs new treatment options.

DR. MENCIA: Certainly there are a lot of broad uses, potentially, for brentuximab based on the data that we’re seeing. Let’s jump now to something you mentioned earlier, which are older agents that are being explored in new uses or on new targets. What can you tell us about some of the advances that we’re seeing with the older agents?

DR. COSTA: At the meeting, for example, we saw some examples. I think there were a lot of data on lenalidomide, which of course started off as a myeloma drug and is now finding its way more and more as a drug for lymphoma in general, but particularly for indolent lymphoma. There were very interesting data on what has been called R-squared CHOP, which is essentially rituximab CHOP chemotherapy but with the addition of lenalidomide. In that context, lenalidomide was used for 2 weeks after 3 weeks of typical R-CHOP and in patients with a high tumor burden of follicular lymphoma. The exciting thing is the very high number of responses.

DR. MENCIA: Your group did a very interesting study looking at chemotherapy plus radiation therapy versus chemotherapy alone. What can you tell us about the data that you presented here?

DR. COSTA: Thanks for bringing that up. We have an interest in outcomes research, and these were data on Hodgkin’s lymphoma in adolescents and adults using the Surveillance, Epidemiology, and End Results (SEER) database. We have seen in this country a trend, over the last decade or so, away
from using radiation in early-stage Hodgkin’s lymphoma, and that trend is very well justified. Historically, second malignancies are a very important cause of long-term morbidity and mortality in Hodgkin’s lymphoma patients who survive initial therapy, which unfortunately occur in the majority of them. The first thing we saw was a trend toward omitting radiation. About half of the patients with early-stage Hodgkin’s do receive radiation, even in more recent years, but that has been reduced by about 10% from the initial decade from this period of follow-up. But, perhaps more interesting is that we detected a slightly decreased survival in the patients who did not receive radiation, even when you adjusted for all the variables. The omission of radiation perhaps had a disadvantage on survival but it did not appear to have any impact on second malignancies, because the rate of cumulative second malignancies seems to be nearly identical.

DR. MENCIA: This has been a great discussion Luciano, and we’ve certainly gone over a lot of data. Let’s try to sum this up. How would you categorize the key messages that the practicing community of hematologists and oncologists can take back to their offices from this ASH meeting?

DR. COSTA: Absolutely. I think there were a lot of things that we were taught here, but there are little data that are ready for use. I think that the general message that we can take from the meeting is that it’s going to become more and more relevant to have adequate, proper pathology. CD30, for example, has been mostly a curiosity in large cell lymphoma with no practical implications whatsoever; we can see that changing in the near future. I think that a proper diagnosis remains essential. Another important message—an eternal message—is that we all need to go above and beyond to enroll patients in clinical trials.

I think there is excitement in essentially every single lymphoma category, with new agents becoming available that are potentially paradigm changing. I think that the revolution we are seeing and are going to see in the next few years in mantle cell lymphoma, CLL/SLL, and even follicular lymphoma is tremendous. I think what we’re about to go through in the next 5 to ten 10 or so is very similar to what we went through in the early 2000s with the advent of monoclonal antibodies. It is important that we go above
and beyond to feed the relevant trials with patients. I think this would help to advance the field forward. There are so many exciting trials of possibly some more practical agents, but these agents are not yet available. I think that it’s important to choose your treatments wisely for patients at a time when a lot of these agents are still not ready for use, still not available, and still not approved. Don’t burn any bridges and perhaps move away a bit from extremely toxic treatments that can lead to long-term myelotoxicity and can impair your patient’s eligibility for a trial in the future or even to receive those drugs or those combinations as the standard of care.

DR. MENCIA: Thank you Luciano. I appreciate your time today and thank you for this wonderful discussion.