Managing Hodgkin Lymphoma

Hodgkin Lymphoma in the Elderly

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Hello, my name is Dr. Andy Evens. I am professor of Medicine at Tufts University School of Medicine and director of the Lymphoma Program at the Tufts Cancer Center. I am reporting live from the 12th International Conference of Malignant Lymphoma being held in Lugano, Switzerland, here in June of 2013. I have been charged with discussing the topic of elderly Hodgkin lymphoma. It is often known in the literature by elderly Hodgkin lymphoma more contemporarily discussed or named as Hodgkin lymphoma in older patients. Historically, that has been defined as Hodgkin lymphoma or Hodgkin's disease recurring in patients aged 60 or more, and it is a topic that had been published on to a decent amount in the 1980s and 1990s, and since that time and even before, it has been fairly well documented that the outcomes in older patients with Hodgkin lymphoma are not just significantly inferior to younger age groups but really disproportionately more than you would expect than just age as a prognostic factor and especially when comparing it to other cancers and other lymphomas. In those studies in the 1970s, 1980s, and 1990s, the difference or the inferior in terms of outcome was decreased by about 40 percentage points, sometimes 50 percentage points with 5-year disease-free survival rates in the 30% to mid 40% range, and it is one that cannot merely be explained by older age. when analyses were done at that time as well as a recent analysis we performed, it is far inferior to controls when you match for age and sex, quite disproportionate as well to normal controls without Hodgkin lymphoma. And so an obvious question is why is that? And there is not one right answer. There are several hypotheses. One certainly is due to the age and likely increasing comorbidities, patients are not able to tolerate therapy as well, and you are not able to maintain the quite dose intensity of chemotherapy, which we are fairly confident is important in most hematologic malignancies including Hodgkin's lymphoma. And also accordingly, there are increased toxicities and really increased treatment-related mortality, and that is one item that sometimes you hope it does not get buried under the rug, but it is in any, especially elderly Hodgkin lymphoma paper, that is one of the first things that I will look at, is what was the treatment-related mortality rate because certainly lymphoma and Hodgkin's lymphoma and the treatments are not a cancer or disease that we associated mortality due to treatment, but that is an important factor. Finally, some authors have suggested is it a different disease compared to younger patients? In other words a

different biology, and there is some indirect data supporting that through those studies, and when looking at analyses before year 2000, some of that clinical pathologic data that was shown was a higher incidence of mixed cellularity, subtype Hodgkin lymphoma in older versus younger patients where it is much more commonly nodular sclerosis, and other factors such as altered performance status, a lower incidence of bulky mediastinal disease. In most of the elderly series, it is 2-3%, at most 5% of older patients have a bulky mediastinal presentation, which is much lower than you would expect in a younger patient population, especially patients in their 20s and 30s, and also a higher incidence of advanced-stage disease. In most of these older patients, it is anywhere from 60-70% of older patients presenting with advanced stage disease. Where in younger patient populations, it is almost in the 50/50 range, even sometimes 55-60% early stage, first advanced stage. So those are some of the background differences that has led us into the contemporary era, at least in the last 10 to 12 years, where there was a bit of a 10-year period where there was not much data, and now in the last couple of years, there has been several publications from our group and others that have looked, has there been an improvement in outcome in these patients, number one, and number two, are there any prognostic factors that we can begin to identify patient populations who have better versus worse outcomes? In terms of the recent studies in the subgroup of older patients with Hodgkin's lymphoma, there was a SEER database analysis by Brenner and colleagues about 5 years ago in *Blood* where they posed the question, has there been "catch up of older patients with Hodgkin lymphoma"? And a quick answer was in looking at 5-year survival curve from the 1970s to about the late 1990s to 2000, there was catch up. In other words, outcomes had improved for older patients with Hodgkin lymphoma, which was good. The other side of the coin was if you look at that 5-year survival rate in the 1970s in SEER, it was 20%, which was somewhat low, so it did increase to a 5-year survival of 40-45%, which is the good news. But I guess the bad news is still when you compare it to older age groups, and not just age groups in their 20s and 30s, the comparative contemporary survival rate, 5-year survival, for patients in their 20s and 30s, was around 90%, whereas even in patients 45 to 59 years, so just one age group down, it was still 20-30 percentage points higher than the age group over 60%. And again, a question about that is why, and going back to some of the treatment regimens, I think a big part of it in several of us who have been looking at this certain patient population has been the particular regimens that are used, and obviously, one of the most common regimens is ABVD, and we think of a relatively well-tolerated regimen, especially for patients in their 20s and 30s who receive treatment every 2 weeks, usually stay on time. I rarely give growth factor despite neutropenia in those patients and they do great. I think the problem is over age 60, there is definitely a problem, and if I had to pick one of the four drugs where there is the biggest problem in older patients is the bleomycin and it is a concern. Obviously, the salient issue is bleomycin lung toxicity, and I think it is a major issue. One, I think it is a little

underrecognized and number two, it is a severe potentially fatal toxicity. In prior ABVD reports, the risk in older patients is anywhere from 20-50%, and that is just bleomycin lung toxicity, and then if you look at patients who have bleomycin lung toxicity, the mortality rate is anywhere from 20-50%. And as anyone can appreciate who has had a patient die of this, it is a pretty severe consequence obviously and it happens often when a patient is in remission, and so, going back to what are some other contemporary studies, we were involved with two studies. One was a retrospective analysis is when I was at North Western in Chicago, we had cobbled together 95 cases of older patients treated from year 2000 to 2009, and what we had aimed to do was to look at outcomes and prognostic factors hoping comparing to older data there had been some improvement. We actually had found survival rates pretty similar to the Brenner looking at series I had alluded to before, 5-year overall survival in the mid 40% range, so still in my opinion somewhat disappointing and that was including some early stage. If you looked at just advanced stage patients over age 60 with Hodgkin's lymphoma in this somewhat population-based survival series, it was around 34%, so pretty disappointing. We also identified that the rate of bleomycin lung toxicity was 33%, and of those patients who developed, BLT, bleomycin lung toxicity, the mortality rate was 31% and was some of the highlights in that series. Now, what we also showed in that, interestingly, was the response rates were pretty decent. The overall response rate was in the upper 80s and the CR rate was 75%, so which is probably a little lower than younger patients wherein younger patients you would expect response rate of 95% and a CR rate close to that 85-90%, so it was not a decreased response rate, at least a period in this retrospective series, looked to be toxicity was a major issue. Now, in that series also, we performed a univariate and multivariate analyses. Interestingly, the International Prognostic Score, otherwise known as Hasenclever and Diehl index, has actually never been validated in older patients, and talking to Volker Diehl on that publication, interestingly only 9% of patients in that large multi- thousand Hasenclever and Diehl were over age 55, and moreover, 0.0 patients were over age 65. So I would fare to say that index as widely used and applicable in many patients is probably not applicable to older patients, and we were able to confirm a few in univariate, but the two factors that were strongest in multivariate were loss of activities of daily living, ADLs, and age over 70, so 60 to 70 versus 70 and above, and moreover, we performed what is called a cart analysis where if you have zero, one, or two of those factors I just alluded to, the survival got worse and worse. In fact, if you are age over 70 and had loss of ADLs at presentation, your 3-year survival is 0%, and these were patients that were treated with curative intent with chemotherapy. So, those were the key findings there.

A more recent publication I was involved with was recently published in the *British Journal of Hematology*, and that was a subgroup analysis off of the large North American intergroup study known as ECOG-2496, and if you recall, that was the study

that over 800 patients that randomized to standard ABVD or Stanford V, and as you probably know, it was published last year in the JCO by Leo Gordon showing essentially no difference in all patients. So we went to look at how many patients were over age 60. Interestingly it was only 43 patients, and so that is another factor I should have mentioned before. The group of older patients with Hodgkin's disease is extremely underrepresented in clinical trials. When population studies are done, whether in the US and Europe, older patients over 60 constitute of anywhere from 15-30% of the Hodgkin lymphoma population, but most studies have included only typically 5%, so very underrepresented. Nevertheless, we took that 5%, those 43 patients, and analyzed them looking at survival and toxicity amongst themselves across the two chemotherapy regimens and also compared it to younger patients, and the high-level findings there were, one, no difference, also in older, just like the large patient population between ABVD and Stanford V in terms of long-term 2-year and 5-year event-free survival and overall survival. But in comparing to the younger, and I guess not surprisingly, still significantly inferior compared to patients less than 60, and still 40 percentage points lower versus the age group in terms of event-free and overall survival. So I think the summary in terms of the survival of older patients is yes they probably improved a little since the 1970s and 1980s, but still disproportionately inferior. We also found in this, and this was obviously a prospective study albeit a subgroup analysis, that we also looked at bleomycin lung toxicity. It was not as high as in our retrospective series which was in all-comers, but it still was 26% incidence of bleomycin lung toxicity with a mortality rate of 21%, so still unfortunately a prominent side effect, number one, and number two, a potentially fatal side effect. Now, we tried to dissect, so there were 11 patients of the 43 who had bleomycin lung toxicity. We tried to dissect were there any predictive factors? We looked at different ages. We even had baseline pulmonary function tests, DLCO, we had a MUGA ejection fraction, did a cardiac function seem to affect that, tobacco history, comorbidities, and unfortunately, really nothing was able to predict it. In fact, five of those patients were nonsmokers, DLCO did not predict, and so a little frustrating that we could not find a factor. I should mention of the 11 patients, 10 received ABVD. So that regimen was probably the only factor that was associated with bleomycin lung toxicity. No other big differences, maybe a slight neuropathy increase in GI toxicity in the Stanford V in those elderly patients. And so I guess in summary, how do I treat older patients with Hodgkin lymphoma? Obviously carefully. I think I have been one and there have been others who have questioned do we need bleomycin at all in Hodgkin's lymphoma? George Canellos had published a letter in the JCO of a lookback at CALGB trials. It has never been done. There actually are prospective trials. The UK, United Kingdom's, current advanced stage randomized trial for patients with a negative PET scan after two cycles will drop bleomycin, so at least that will be a randomized trial to look at that. But for most patients, certainly over age 70, and in select patients, I might include it from 60 to 70, but I will leave just a priori, not give bleomycin to those

patients. I just deem it as the risks outweigh the potential benefits. And so what are two regimens that I have used off of a clinical trial? One is just AVD, in other words, ABVD without the bleomycin, and another regimen that was a small publication in 2007 was good old-fashioned CHOP. The last author was Kolstad in 2007. It is a small study. It was only 26 patients with older elderly Hodgkin lymphoma, but they showed survival rates exceeding 65%, so small, but we know CHOP is generally tolerable, so I have often vacillated between those two regimens. The other subtext there is there have been other data showing that growth factor, GCSF whether Neulasta or Neupogen, increases the risk of bleomycin lung toxicity, and so that has never been shown prospectively, but now if you are not giving bleomycin with a little more impunity, you are able to use growth factor in those patients. Finally, I will mention there are clinical trials that have addressed this patient population, specifically older Hodgkin lymphoma, two recent publications, phase II trials, one regimen called PVAG published by the German Hodgkin Study Group and a second from the United Kingdom, Steven Proctor, which was called VEPEMB, and they showed decent outcomes in the 50-60%, so unfortunately, not homeruns on either of those looked to be okay, still was a treatment-related mortality rate in both of those trials. I should have mentioned back in the ECOG-2496 there was a treatment-related mortality of 9.3% in the older patients versus 0.3% in the younger patients, so that was significantly increased. There were two bleomycin lung toxicity deaths due to ABVD, and in the Stanford V, there was a GI bleed sepsis and a pneumonia sepsis as well in that study. But finally, there are clinical trials also incorporating novel agents. I am happy to be part of the study that is incorporating brentuximab vedotin, or Adcetris, in the older patients with untreated Hodgkin's lymphoma, and actually it is a window study where we are starting with two doses of brentuximab vedotin and then proceeding what we consider current or standard chemotherapy, AVD without the bleomycin, and then giving another four doses of brentuximab vedotin, and that is open at 7-8 centers across the United States, Memorial Sloan-Kettering, MD Anderson, Ohio State, Stanford, and other sites as well. There also is a concurrently running single-agent brentuximab vedotin trial for patients with untreated Hodgkin's lymphoma, so hopefully that by incorporation of novel agents that are effective, yet more tolerable, will really help us improve the outcomes for these patients. Thank you for your attention and please be sure to view other highlights from the 2013 ICML meeting.