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Real-World Treatment Effectiveness Compared with Clinical Trial Efficacy in Multiple Myeloma: A Focus on the EU

Announcer:

Welcome to CME on ReachMD. This activity, titled Real-World Treatment Effectiveness Compared with Clinical Trial Efficacy in Multiple Myeloma: A Focus on the EU, is provided in partnership with AGILE and is supported by an independent educational grant from Thermo Fisher Scientific, Clinical Sequencing Division.

Before beginning this activity, please review the disclosures and learning objectives.

Here's your host, Dr. Ken Anderson.

Dr. Anderson:

Clinical trials are a necessity for the development of any new treatments, but unfortunately, the outcomes of these trials don't always match up with the experience of patients in the real world. That's exactly the current situation of patients being treated for multiple myeloma, which is why we'll be exploring the broad implications of this discrepancy, and even more importantly, how this can be corrected.

This is CME on ReachMD, and I'm Dr. Ken Anderson. Joining me in this discussion is Dr. Philippe Moreau, Professor of Hematology at the University Hospital Hôtel-Dieu.

Dr. Moreau, thanks for being here today.

Dr. Moreau:
Thank you, Dr. Anderson.

Dr. Anderson:
So, before we really dive in here, can you frame this issue for our learners including whether these differences in clinical trial and real-world outcomes exist in both the academic environments as well as in the community-based oncology?

Dr. Moreau:
So, this point is very important, both for the clinicians but also for the patients. And we know that when a patient is enrolled into a clinical trial, this patient is selected according to very strict inclusion and exclusion criteria, and therefore, in many clinical trials the patient population does not represent exactly what is the patient population in the real world. For example, we are very often excluding patients with renal impairment into clinical trials. We are also excluding patients with a poor performance status. Some classes of agents cannot be used systematically when patients have a poor performance status or if they have a preexisting peripheral neuropathy. Some data published recently are showing that in the real life the outcome of patients for response, for duration of response, for overall survival as well, may be inferior to the outcomes that are frequently described into clinical trials.

Dr. Anderson:
Thank you very much for setting the stage for us, Dr. Moreau. So, in August 2018, there was a study published from the German Tumor Registry Lymphatic Neoplasms, or TLN, that provided further insights into just how different treatment outcomes are for patients with myeloma who are treated in a real-world setting versus a clinical trial setting. Can you please discuss those data and the broader implication of these data for patients in the EU?

Dr. Moreau:
Yes. This study was published by Dr. Knauf and colleagues in Germany in... 2018. They recruited 285

patients that were not eligible for stem cell transplantation with symptomatic myeloma. At the start of the front-line treatment they categorized patients into 2 groups: patients that presented with at least 1 common exclusion criteria for clinical trials, heart or renal failure, liver or renal disease, peripheral neuropathy and HIV positivity. All other patients were considered potentially trial-eligible. And they compared the outcomes of patients that were potentially trial-eligible versus those patients that could not be potentially enrolled into clinical trials. In fact, they showed that 30% of the patients were classified as trial-ineligible. When you are looking at the outcome for both progression-free survival and overall survival, there is a huge difference for patients trial-ineligible versus patients trial-eligible. The progression-free survival was 16 months when patients were trial-ineligible versus 27 months for the larger group of patients. The median overall survival was 34 months, so less than 3 years, versus 58 months, so roughly 5 years for patients trial-eligible.

Of course, the data were collected quite a long time ago, from 2009 to 2011. The data were collected in more than 80 centers in Germany, indicating that potentially only 4 to 5 patients were collected in each center, so we had also some bias into this study for sure. But the study demonstrated at the time of diagnosis, if you are not eligible to receive what is standard of care, or you have to adapt the dose; you have to discontinue treatment based on toxicity; the performance status is also impacting the dose intensity of the combinations that you would like to use, at the end of the day, the outcome of the patients are inferior for PFS, but also for overall survival.

Dr. Anderson:

Yes, I think that's so important, and I think the implication, Philippe, of these findings for patients in the EU is to use great caution, because fully one-third of the patients that are described in the big Phase III clinical trials really are not relevant for the patients that you see in practice in the clinic—very, very important indeed. And you have talked about some of the root causes for this discrepancy, but did you want to mention any other key differences between clinical trial settings and real-world settings?

Dr. Moreau:

Of course, in Europe, we have to stick to European guidelines. Currently, for the group of patients that are not eligible for stem cell transplantation and the standard of care that we are using is either the combination of bortezomib/melphalan/prednisone, the BMP regimen; or more and more the lenalidomide and dexamethasone combination, LenDex; or, as well, BLD, the combination of bortezomib, lenalidomide and dexamethasone. And we know that we cannot use, for example, bortezomib in patients with a preexisting peripheral neuropathy. We know that in case of renal impairment, we have to be careful with the dose of lenalidomide and we have to adapt to adjust the dose of this very good drug. We have to inform, in fact, our colleagues in the community-based hospital where the expertise in myeloma is not as important, for example, a large university hospital with a big

hematologic department fully dedicated to patients with myeloma. We have to educate physicians and oncologists, hematologists, how to use a specific combination, how to decrease the dose, how to try to use frailty assessments before proposing a specific combination. So, these data are really, really important. We don't have only to mention that this standard of care is combination A or combination B at full doses. We have also to take into account in each of our educational talks about those important data and including a subanalysis, on how to treat patients that are presenting with renal impairment or some exclusion criteria for clinical trials.

Dr. Anderson:

Thank you very much. For those of you just joining us, this is CME on ReachMD, and I'm Dr. Ken Anderson. I'm speaking with Dr. Philippe Moreau about multiple myeloma and the discrepancies that exist in treatment outcomes for patients in clinical trials versus a real-world setting.

So, now, Dr. Moreau, let's talk about some of the possible changes that could be made in the EU, both in clinical trial design and in patient-centered choices that could improve the short- and long-term burden of treatment and, importantly, improve the overall outcomes across all settings.

Dr. Moreau:

So, that's a very interesting but very difficult question. For example, in trials dedicated to elderly patients, we have to try to enroll a significant number of patients above the age of 75 years that are representing a very important group of patients, knowing that the median age of multiple myeloma in Europe is roughly 72 years at the time of diagnosis. We also have to modify inclusion criteria based on renal function and not excluding patients with creatinine clearance of less than 40 mL per minute, and to accept patients with moderate renal impairment, with creatinine clearance above 25 or above 30 mL per minute, so that will be very, very important to generate clinical trials that create data that are really close to the real-world patient population.

We also have to inform the patients about the potential toxicity of specific combinations and try to use the combinations that are safer and that can be used in patients with poor performance status or that are living far away from the hospital—oral combinations, if possible. We know that, for example, ixazomib is a drug that can be safer delivered to elderly patients in the relapse setting. Ixazomib is approved in combination with lenalidomide and dexamethasone. And we know that that's an old oral regimen that is really convenient for patients. Ixazomib is not affected by renal impairment, etc. So, we have drugs like that that are available, that are safe. We have to use weekly bortezomib, for example, instead of bi-weekly in case of a preexisting peripheral neuropathy.

So, we have to educate—that's very, very important—and try to define combinations: for example, the VRd light regimen with the 15 mg of lenalidomide instead of 25, with weekly bortezomib instead of

biweekly, with cycles based on the 35 days instead of 21 days. And at the end of the day, when you are looking at the results of the Phase II study with VRd light, for example, the median progression-free survival in elderly patient's front-line treatment is roughly 36 months. That is very close to what can be achieved in other patient populations with full doses of treatments.

Dr. Anderson:

Thank you very much. That really highlights the importance of thinking about the real-world patient and the fact that you can make modifications in order for patients to appreciate the benefit of these treatment advances. So, before we close, is there anything that you'd like to revisit or discuss that we haven't touched upon today?

Dr. Moreau:

Yes. In fact, just one point to highlight, that the German study looked at patients eligible or not eligible for a specific clinical trial, but we also have to generate real-world data with each of the new combinations that were recently approved outside clinical trials. We need to try to reproduce with the old consecutive patients that are coming into our departments, into our units—as a result, for example, with daratumumab single-agent in very advanced patients to look at the progression-free survival is identical to that was published into the (inaudible)*17:49 study for approval, which is also true for all the new combinations with lenalidomide, dexamethasone or ixazomib or other drugs or other regimens, and that will be very, very helpful, in fact, in your daily practice in each of our hospitals.

Dr. Anderson:

So, Dr. Moreau, I think you have beautifully summarized for us and highlighted how clinical trials data does not often reflect real-world practice and fully a third of the patients in this German study that were reported had inferior outcome and really would not have qualified for clinical trials. The patients we treat with myeloma have comorbidities that simply make them ineligible for trials, and you really stressed for all of us the importance of clinical trials that actually treat patients that we see in the real world as one solution to this problem. And then a second solution is the collection in patient registries, large databases, of the treatment outcomes and side effects that occur in patients in the real world.

Dr. Moreau, it was great speaking with you today. Thank you very much.

Dr. Moreau:

Thank you, Dr. Anderson. Good to speak with you as well.

Announcer:

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