Transcript of Rai Interview Part 3: CLL Treatment

Gerald Marti: Thank you. I think that the progression that I was thinking in my mind was that the possibility now that I remember many years ago Lee Nadler, when he was visiting here, used the term paradigm shift in CLL and in his era, I'm going to say the 1980s or perhaps a little bit later, we began to hear the difference between palliative treatment in CLL versus the possibility of cure, something more than palliative. Now, recently there has been some discussion that early treatment in CLL, Rai stage I or II, Binet stage A, particularly if they're symptomatic, that those patients might have as good a survival or even better overall survival than the traditional treatment of a Rai stage III or IV or Binet stage C. Would you comment upon that?

Kanti Rai: This is a very relevant and important question. That is, is there truly a paradigm shift from our therapeutic end point, which was clearly in the earlier decades, was of palliation because we did not have a cure. If you do not have a cure, then it is not right, not fair to make a patient suffer with aggressive treatment, the toxicities that can come with myelosuppression, immune suppression and other non-hematological toxicities of aggressive chemotherapy. With the observation that 69% of front-line treated CLL patients achieved complete remission with FCR, and if you be more restrictive and use 40% CR with the multi-institutional observation with FCR or FR, then you have to expect that the life expectancy of CLL would be improving.

And that exactly happened. That is the data of Dr. Keating initially showing that FCR treated patients had a much longer life expectancy than any other treatment regimen. But again, because it was a single institution, non-comparative historical control for comparison purposes, so the community of investigators outside MD Anderson were not readily accepting. But then John Byrd did a comparison of [CALGB] 9712, the FR results with [CALGB] 9011, the F versus chlorambucil that we earlier talked about, and demonstrated that indeed the FR trial led to somewhat longer life expectancy for the CLL patients. So, that has led for people treating CLL to change their therapeutic end point to prolongation of life while maintaining good quality of—of preserving quality of life as our therapeutic end point.

But there are other colleagues who are treating CLL, are already using the word "cure," which I shied from using because we are hoping to get to that point, but in my opinion, we are still far from that target, and that is to find some people to be cured. And yes, no question that some survivors of allogeneic stem cell transplantation are indeed alive and well and without evidence of any disease and they can be considered cured, but those are an extremely small minority of CLL

patients. So, that the paradigm shift is from palliation to complete remission achievement. And that now is leading to, from after achieving complete remission, whether we should go for elimination of evidence of minimal residual disease. That is a paradigm shift.

Marti: And I think even that's an era of something that's happened about standardization of detecting—determining minimal residual disease. That seems to be an effort perhaps stronger in Europe than here. That's an ERIC endeavor led primarily by Andy Rawstron and Peter Hillman, I believe for the ERIC group, although I think we'll begin to see—well, I think we already have minimal residual detection in this country. I'm not so sure it's as standardized as it is in Europe. I don't know how you feel about that.

Rai: I agree with you. I think that the pursuit of minimal residual disease identification and the standardization is much stronger in the UK and some parts of Western Europe than the US, although there are groups in the US which are pushing for MRD. I have nothing against MRD. I'm hoping that I will feel enthusiastic about MRD, but I'm waiting for the time when MRD determination will become meaningful. Because most of the time that we have, our patients achieving a remission, we still have evidence of disease by flow cytometry. And yes, they have excellent quality of complete remission by clinical criteria, but if we cannot feel satisfied that the disease has totally gone away, then to put expensive testing to show how many CLL cells are still lurking in the CR patient, to my mind is an exercise in theory.

I would like to reach a point where it becomes meaningful. Already we are showing that those who have clinical complete remission go on to live a longer life. But to get a large enough number of patients who are MRD negative and then demonstrate that those patients are the ones who are cured, by watching them for four or five years when there is no evidence of minimal residual disease and there continues to remain no evidence, then I feel that going after measuring MRD is reasonable and justified. But if people are excited about this, I will not criticize them.

Marti: What about the role of Campath treatment in minimal residual disease in this country?

Rai: I think that Campath is a very appropriate drug or monoclonal antibody to attempt elimination of minimal residual disease. But what we do not know is whether in those patients who have achieved a complete remission by clinical criteria and still have some evidence of disease by minimal residual disease criteria, whether we have to give the same 30 milligrams three times a week dose of Campath or alemtuzumab, or a smaller dose or less frequent dose will be adequate

because we must remember that alemtuzumab comes with a threat of CMV conversion from negative to positive and even CMV disease, either hepatitis or pneumonia, and other problems of immune suppression types.

Therefore, I feel that we owe it to our patients to conduct either randomized or prospective, not necessarily two-armed comparison study, to demonstrate that a different dose of Campath or alemtuzumab levels have been tested and one out of those turns out to be superior and non-toxic. So, I think that on theoretical basis, alemtuzumab is an ideal agent to be tested, but I wish that we knew what is the safest and most appropriate regimen would be.

Marti: Okay. Well, I think that one other thought in terms of the treatment of CLL is that if you can establish CR with or without minimal residual disease, you may be able to create a chronic disease that may be treated with something like Revlimid at monthly intervals, or say Rituxan, the lymphoma dose, four doses, weekly, for a month, every six months. What role does that have in CLL?

Rai: An extremely important question, because I agree with you 100% that what we are moving towards, if not a cure—as you reminded me that Lee Nadler used the words for the first time in CLL—a paradigm shift. Going to the example of a chronic myelocytic leukemia and emergence of imatinib, which has caused a paradigm shift, that CML by this targeted successful therapy of Bcr Abl target has become instead of a death sentence for the patient, has converted CML into a chronic disease. Chronic disease such as diabetes, Type II diabetes. Those patients can go on and on if their blood sugars are well controlled in diabetes, and hemoglobulin A1C is in a very safe normal range, then they do not suffer from the long-term stigma of diabetes, the eyes and the heart and atherosclerosis and what not. And instead of being a fatal disease, it has become a chronic disease, with which patients can live.

Similarly, CML, as long as the patient is taking imatinib, he does not have to fear that the death is around the corner. And we have known that now that imatinib has been in existence in clinical medicine for approximately nine or 10 years. But there are indeed large numbers of CML patients going on with a molecular complete, cytogenetic complete remission and no evidence of disease, and taking their pills and going on in a good quality manner. So, we are hoping that we will convert CLL, also a chronic disease, and FCR and FR have already put us on that track. And now as you earlier mentioned, if we can get a safe dose, a small dose infrequently given, as frequently as three times a week or less than that, or an immunomodulatory drug such as

lenalidomide, which also can take care of minimal residual disease, then if we demonstrate by clinical trials that that is visibly safe and effective, then we have a conversion of CLL from a death sentence to a chronic disease.