Transcript of Rai Interview Part 2: Clinical Trials

Kanti Rai: So, coming back to the trial that you are mentioning, the CALGB study[1] of fludarabine versus chlorambucil, and the previously treated patients with CLL became an important question. It required a lot of planning and my recollection is that the planning process itself was approximately one year. And again, I must say that there were a number of colleagues who helped me in planning and developing that study. First was Charlie Schiffer, who was the chairman of CALGB's leukemia committee, was immensely helpful in guiding me in this study, and Dr. Holland, again[2].

And it was really a matter of convincing the practicing oncologists who were associated with all the academic institutions participating in CALGB to put their patients on, because when they saw a patient newly diagnosed to have CLL, they would treat with chlorambucil and they felt comfortable with that. And this study required them to think about CLL and not to be automatic because at that time, we did not even have the guidelines as to when to start a patient with CLL on some chemotherapy.

And if you remember, that the guidelines developed by Dr. Cheson as National Cancer Institute has sponsored working group on CLL, who had come out just then—the first report was in 1988[3] and this study was initiated approximately at the same time. So, we were doing two things. One was to make the practicing hematology oncology community become aware of formalized guidelines as to when the treatment of a previously untreated CLL patient was considered appropriate and then to give either one of these two drugs for whatever the patient was randomized to, in a disciplined manner: watching the guidelines of the protocol about adverse events, toxicities, adjust the dose because the treatment was recommended for a period of one year. And during that time, a patient, for example, could go from a starting white cell count of 200,000 to 2000 or hemoglobin, wherever it was. And the doctors were required to pay attention.

And that was an experience. I had to carefully look for the flow sheets[4] coming from those patients and we had, at the end of the day,

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[1] Dr. Rai's note: This trial is not at all relevant today.
[2] Dr. Rai's note: Arthur Sawitsky also provided assistance.
[3] Cheson BD, Bennett JM, Rai KR, et al. Guidelines for clinical protocols for chronic lymphocytic leukemia: recommendations of the National Cancer Institute-sponsored working group. *Am J Hematol*. 1988 Nov;29(3):152-63.
[4] Dr. Rai's note: In those days of paper flow sheets, things were different. The PI's role was crucial.

approximately 500 patients randomized to this study. And it was an enormous responsibility to make sure that patients did not suffer adverse effects which were preventable and if there was an adverse event, then make sure that that patient stopped taking whatever the randomized drug was and be watched before reinstituting treatment.

So, that paper was accepted for publication by the *New England Journal of Medicine* and it came out in that journal in 2000.[5] And it was very widely received and considered to be an important contribution because this showed that indeed fludarabine proved to be a superior drug to chlorambucil in inducing a higher percentage of remissions, particularly higher—significantly higher—percentage of complete remissions. But the duration of survival with fludarabine-treated patients was not significantly longer and that was some kind of a disappointment, but nonetheless, that is how the results were and it became a standard in terms of CLL front-line treatment for the next couple of decades.

Gerald Marti: I think that's a good summary of that landmark study and one in terms of looking at the history of the treatment of CLL. It would be more exciting to go forward from that but before going forward, I know that you were also involved in some of the early studies looking at daily versus intermittent chlorambucil and combined with prednisone. Would you comment on that as an era between the beginning of chlorambucil, which we usually attribute chlorambucil at least to the introduction to Galton—you can certainly comment about that too—but I know that you and Dr. Sawitsky looked at that question in several papers.

Rai: Yes. That is indeed a very important historical prelude to the fludarabine-chlorambucil randomized trial. And that was again in CALGB and this was in the 1980s and you mentioned Arthur Sawitsky. Arthur Sawitsky was my mentor, my teacher who indeed in the 1950s essentially picked me out to train in hematology, taught me all what I know in diagnosis and treatment of hematological disorders, be they erythroblastosis fetalis, Rh incompatible babies coming with icterus and kernicterus and whatnot. This is the era going way before RhoGAM was invented and protected the Rh-negative mothers from being sensitized with the Rh-positive babies in utero and those babies used to really either suffer, or die, or double up kernicterus and brain damage from that.

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[5] Rai KR, Peterson BL, Appelbaum FR, et al. Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukemia. *N Engl J Med*. 2000 Dec 14;343(24):1750-7.

And he showed me how to do exchange transfusions in the neonatal nursery to showing me how to treat leukemias, acute leukemia in children and then in adults. And Arthur Sawitsky as my mentor introduced me to CALGB. And in the 1960s as you pointed out, chlorambucil had just been introduced, first by Dr. David Galton in London and then others. Particularly the ECOG and Southwest Oncology Group had done studies using chlorambucil in front-line and previously treated patients, and Charles Huguley—Charlie Huguley whose name stands out, Bill Knospe's name stands out in those earlier trials. And CALGB under the leadership of Arthur Sawitsky and Richard Silver picked up on those.

And as you pointed out, there was a very important randomized study of chlorambucil being given on an intermittent basis on a large dose with several days in between those doses, all lower dose on a regular, continuous daily basis and both on intermittent chlorambucil or daily chlorambucil had prednisone added to that, and there was a third arm of prednisone alone without chlorambucil. This was an extremely important study and it showed essentially confirming Huguley's and Knospe's earlier work that the activity of both were equal, whether it was given intermittently or on a continuous daily basis.

And the third arm of prednisone alone was inferior to those other arms which contained chlorambucil. And indeed, it showed that the toxicities which many were concerned occurring with intermittent dose did not pan out. And therefore, it was left, the bottom line was that the treating physicians could use whatever they felt was more suitable for that particular patient of theirs, be it intermittent or daily.

Marti: I probably should have started with chlorambucil and worked ourself—worked our way forward but I wanted to draw the comparison between your experience with AML, the seven-three therapy, and how I think that may have helped you, trained you for the fludarabine-chlorambucil study. Since the introduction of fludarabine in that landmark study, we've had even another major change and that's the addition of Rituxan to that combination and you participated in that too.

Rai: Yes, yes.

Marti: How did that come about?

Rai: Well this is an interesting development because rituximab was introduced as you know in the US in the treatment of follicular or low-grade lymphomas and it demonstrated very, very impressive levels of activity in follicular lymphomas. And follicular lymphomas in many

ways are similar to CLL[6]. Both had a reputation that the patients live on and on; they are not the killer diseases as other hematological malignancies such as acute leukemias and diffused large cell lymphomas were known to be. But used as a single agent, rituximab did not seem to have impressive activity in chronic lymphocytic leukemia. Therefore, rituximab was not going anywhere as far as CLL was concerned.

Then came observations in vitro that when rituximab was combined with fludarabine, be they lymphoma cells or CLL fresh cells, that there was synergy, the level of cytotoxicity induced by rituximab alone or by fludarabine alone far exceeded when the two were combined and it was not just the sum of the two but way beyond that. And that led to clinical observations of using rituximab not as a single agent but in combination with fludarabine. And CALGB under the chairman leadership of John Byrd initiated a clinical trial in 1997.[7] And we were not quite aware in CALGB when we initiated the 1997 fludarabine plus rituximab trial that Dr. Michael Keating at MD Anderson had already started a couple of years before, but quietly, a single institution study of combining rituximab with fludarabine and cyclophosphamide.

And so, both FCR and FR, FR, the trial of CALGB and FCR, the trial of MD Anderson came out with the results virtually simultaneously, although the results were first reported on FCR by Dr. Keating ahead of FR results. But people were impressed that both FR and FCR were superior to anything else that CLL patient treatment had known before. And it is important to add here that FC combination had already been picked up by Dr. Michael Grever and the Southwest Oncology Group when they decided that F alone was not good enough, that is, fludarabine alone was not good enough and cyclophosphamide alone was not good enough, but when combined, FC turned out to be superior—significantly superior to F or C alone and not with any much worth toxicities.

So, building on that, that FC was probably the better combination in front-line treatment, Keating added rituximab and showed that with that induced phenomenally higher percentages of complete remission and the results that CALGB achieved also showed that FR was a

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[6] Dr. Rai's note: As far as their respective clinical course and natural history are concerned.

[7] Byrd JC, Peterson BL, Morrison VA, et al. Randomized phase 2 study of fludarabine with concurrent versus sequential treatment with rituximab in symptomatic, untreated patients with B-cell chronic lymphocytic leukemia: results from Cancer and Leukemia Group B 9712 (CALGB 9712). *Blood*. 2003 Jan 1;101(1):6-14.

formidable combination. The reason why the country accepted FR ahead of FCR was that FR results were multi-institutional based, large numbers of clinicians put the patients on this trial whereas by definition patients at MD Anderson, they were not selected or selectively placed by design, but by the very nature of this that if the patients were not local in Houston, Texas, they all had to travel from distant parts of the country and be able to stay for a couple of months in Texas, in Houston.[8]

And therefore, there was a built-in selection of a better-quality patient in the health performance and status basis and probably better economic, social economic basis which Dr. Keating never planned in the protocol itself by design to have that selection. So, a single institution based study of FCR was extremely impressive but the people who were practicing found that even though with FR, the complete remission rate was in the order of about 40% to 43%, whereas the FCR, where the large sample size in Dr. Keating's study was 70% or 69% complete remission. And out of those 69% complete remission, what Dr. Keating showed was that almost half of those 69% of the patients with complete remission had molecular complete remission[9] by flow cytometry or by PCR.

So that established the use of rituximab in combination with chemotherapy, either with F, which is CALGB contribution, or FC, which is MD Anderson contribution.

Marti: And it's my understanding that the FCR combination was actually confirmed by the German CLL study group?

Rai: That's true. Then a number of years later, the German CLL study group led by Michael Hallek did a very good randomized large study,[10] multi-institutional study, in which they compared FC, the prevailing best front-line treatment of CLL, versus FC plus rituximab and demonstrated that FCR was significantly superior to FC, and now this trial was a reconfirmation on a multi-institutional and randomized perspective study basis that FCR was superior. But it is important to know that this large multi-institutional, large randomized trial showed that FCR indeed had significantly greater complete remission, but they did not—that statistic did not reach anywhere what the 69% complete remission that we obtained in Dr. Keating's trial.

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[8] Dr. Rai's note: These were single-institution based data.

[9] Dr. Rai's clarification: no detectable residual disease

[10] Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet*. 2010 Oct 2;376(9747):1164-74.

Marti: Single institution.

Rai: Single institution, 69%, multiple institution was 40, 42%, which is what FR of multi-institution, of CALGB also had reached. So, on the basis of that German randomized study showing FCR was significantly superior in complete remission, overall remission, and remission, duration, and progression-free survivorship that the US FDA recently, in the earlier part of 2010, approved FCR or Rituxan in combination with FC chemotherapy as a treatment for CLL in front-line.