Dr. R. Kurzrock / ECD Global Alliance Teleconference
7/16/08 10:15 – 11 am Central Time

Dr. Kurzrock Background:

UT M. D. Anderson Cancer Center, Houston, TX
Chair, Professor of Medicine
Department of Investigational Cancer Therapeutics

Research Interests: New drug development: personalized cancer therapy, molecular oncology

The long-range objective of my research is to identify the molecular profile of tumors and match the abnormalities with specifically targeted therapies to which patients with cancer are most likely to respond. We now have the largest program of phase I cancer clinical trials in the country and we concentrate on novel molecules for advanced cancer.

For more information, please see: http://gsbs.uth.tmc.edu/tutorial/kurzrock.html

Teleconference Attendees:

Dr. Kurzrock
facilitator
10 ECD patients and caregivers

Transcription of Teleconference:

After each attendee gave the group a brief introduction of themselves and how they were affected by ECD, the conversation turned to listening to what Dr. Kurzrock had to tell us about her experience in treating ECD. Dr. Kurzrock preferred to answer the list of questions that were sent to her in advance. The following shows the pre-prepared questions in bold with Dr. Kurzrock's answer following. Questions that are not in bold were asked during the course of the conversation.

1. **Do you have a recommendation on the dosage of interferon that patients should take as a general rule? Do you suggest a higher dosage 3 days/week or a lower dosage every other day? Is there a maximum dosage that is recommended? Should the dosage be reduced to a specific minimum if good results are being seen?**

I wouldn't mind getting some feedback from those with individual experiences with the Interferon. But I will explain our experience with Interferon here. Some of the initial uses for interferon were developed at MD Anderson Cancer Center. Studies done here were responsible for gaining approval for its use to treat hairy cell leukemia which was one of the original approvals; and also for treatment of chronic myeloid leukemia (CML). In the latter disease, newer more targeted agents have superseded interferon. Each disease treatment uses a different dosage of Interferon. In hairy cell leukemia the doses are 3mu 3x week. That is a relatively lower dose. In CML the dose was 9mu per day. That is a very high dose and was very difficult to tolerate. The hairy cell leukemia dose of 3mu 3x per week is very well tolerated by patients. However, for some peculiar reason, we have found repeatedly that the ECD patients tolerate even the lower dose very poorly. It's a rare disease so we didn't treat hundreds of patients, only a few patients. We found repeatedly that the ECD patients had a lot of fatigue and depression and other side effects from even the lower dose of Interferon. So we lowered it further to 1mu 3x week. And that seemed to be reasonably well tolerated. At least the first three patients we treated responded to that lower dose. We have now treated 10 or 15 patients (I don't have the number in front of me). and I believe 50% of the patients are responding. I don't know if raising the dose

would increase the response rate. Maybe at a higher dose everyone responds. I don't know. But because it is a chronically administered drug, you can't just take it for a week or two and then quit. I don't think it is really feasible to raise the dose. So I think that patients have to take a dose that is tolerable and at that tolerable dose our experience is that about half the patients are responding.

Q: Is Interferon like chemotherapy?

Interferon is not chemotherapy. Interferon is a natural product that is produced by the body, and has been made artificially. Your body produces it when you have the flu or any viral infection. The word Interferon comes from the word "interfere". It interferes with viruses. When you have the flu, you have a fever and you feel achy? That's because the body is producing Interferon to fight the flu. So those are the side effects: fever, aching, feeling like you can't get out of bed. I think chemotherapy is generally tougher than the Interferon. But with the Interferon, because it is given three times a week, the side effects if you are on too high of a dose can be tough, so we have lowered the dose to 1mu 3x week. And again, in our patients that has been much better tolerated.

Q: Is that the dosage that you start the patients at – 1mu 3x week? Or you do you start them at a higher dosage and then lower it?

I initially started at a higher dose and reduced it because the 3mu 3x week was so well tolerated in our hairy cell leukemia patients. But now if I see new patients I would start them at the lower dose because I've had this experience repeatedly where patients have had a tough time with the higher dose. So I figured I would start the patients at the lower dose and then if they are not having side effects I can always raise the dose.

Q: Is the lower dose as effective at slowing down the progression of the disease?

I don't know if it is as effective as the higher dose. We do know that it is working in about half the patients so we do know that it can be effective. The question would be is if we used a higher dose would it work for more than half the patients, or would it do a better job? That is certainly a consideration, but that is true for all therapies. With many therapies, if you could give higher doses, you would get better results. It is true with chemotherapy, too. If you give a higher dose you get better results, but then you have more side effects. A basic principle of giving treatment is that you have to give a treatment that is tolerable to the patient and is effective at a dose that is tolerable.

Q: If someone started out at a higher dose and had good results would you recommend possibly lowering the dose and keeping it at a maintenance dose?

If the patients don't tolerate it we recommend lowering the dose. If the patient is tolerating the higher dose we would keep the higher dose. We do know that even after patients have been on Interferon for a year or two with good effects, if you stop the Interferon the disease tends to come back. So we have not recommended stopping the Interferon if the patients are responding.

Q: Do you see the Interferon reversing the disease or is it just holding it at bay?

We see it reversing it, although we have not cured a patient. We don't seem to be able to get rid of it altogether, but there is a clear decrease in the disease. Sometimes that can occur very quickly and sometimes it is a more gradual thing. For instance, we had one patient that had a very rapid decrease in the problems he had with the bulging in his eyes. He was about to go blind because of the pressure. We started the interferon and within a month I I could see from across the room that he had had a dramatic response. I've had other patients where it has been much slower. For instance with bone disease over a period of a long time there is a gradual decrease in the bone pain and a gradual decrease in the need for pain medication.

Q: What symptoms does Interferon help with?

If the Interferon works on a patient, our experience has been that it works on all symptoms. Again, you have to find a dose of Interferon that is tolerable.

2. What can you tell us about the fatigue/irritability that comes from ECD and interferon? Do you have any suggestions on how to battle this?

I'm sure there is fatigue and irritability from the disease, but Interferon itself causes irritability. You feel irritable when you have the flu because your body is producing interferon.

Q: Could Interferon take the place of chemotherapy if done correctly?

Yes. With the fatigue and irritability you just have to find a dose that is tolerable and hopefully the patient will respond at that dose. Again, not everyone responds but about half the patients seem to respond nicely. The dose we have found to be the best for the ECD patients is 1mu 3x week.

Q; But you do see results with the dose of 1mu 3x week?

Absolutely, yes. Not everybody, but about half the patients have very good results.

3. Is there a difference between interferon alpha 2A or 2B?

I do not think there is a real difference between those two interferons.

4. Do you think interferon should be continued during courses of cladribine?

No, I do not. If you move on to try cladribine I do not think interferon should be continued. We have less experience with cladribine. We have only treated a couple of patients, although I do think we've seen positive results with it. One of the issues with cladribine is that it is a great drug for the first course. It has almost no side effects, but it really suppresses your immune system if you have to give more than one course. So, if you can give one course and the patient has a good result, then that is great. If you have to give a second course you might get away with it. If you have to give a third or fourth course there is potentially a bad impact on the patient's immune system. I am very wary of giving the third and fourth courses of cladribine. But as a first course, cladribine is a great drug with virtually no side effects. It is just if you have to give it again and again that it becomes a problem.

Q: Do you get good results from using cladribine?

We have only treated two patients, and one of them responded. Now remember, this is a rare disease. Fortunately we do have some of our patients responding to interferon. There are some cases in literature of patients responding to the cladribine, and our very small experience suggests that patients can respond to cladribine.

Q: Referring to what you said earlier about lowering the dose of interferon, if a patient is tolerating a higher dose would you recommend lowering the dose?

I would not recommend lowering the dose if the patient is tolerating the higher dose.

5. Are there any new treatments that are under consideration for ECD? Under what conditions? (eg, pegasys, incyte, inatanib, etc.)

The research in this disease is very limited because it is such a rare disease. Probably pegasys, which is a prolonged interferon, would be something reasonable to try. We have not tried it at this juncture. The other drug that I think is reasonable to try is the cladribine (2cda).

6. What can you tell us about the long term findings of ECD patients taking interferon treatments?

It seems to work for a long period of time, but not necessarily forever. Even if you have been on it for two or three years and you are doing well, if you stop the treatment the disease comes back. We had one patient that had a great response and after four years the disease seems to be developing resistance to the interferon. We have another patient that is still doing well after several years. We do not seem to be able to cure the disease. There is definitely a lot of improvement but the disease is still there. Our experience shows that for those patients who respond to Interferon, it seems to control the disease for a long time. This time frame is measured in years, but it doesn't seem like it will work forever. At least in some patients the disease develops a resistance, and we may have to think about doing other things. This is something we are just learning about now.

Q: Will there be follow up literature on the ECD studies that have already been published?

We published one case first, and then we published three patients treated with interferon. Usually we don't publish just three patients. It is usually at least 20-30 patients in a published study, but because the patients did so well on the interferon we wanted that information to be in the literature. We have now treated about 10-15 patients. We would like to put together a publication, but I think it will be at least a year before anything else is published because it is still a small experience. With what I have told you so far you are probably as up to date with our experience as anyone else in the world.

Q: How did you treat the 50% of the patients that did not respond to the interferon?

The 2cda is the only other treatment we have tried. We tried that on a couple of patients. About 3 of our patients were lost to follow-up, and 2 of the patients have died. As far as the follow up, you have to remember that our patients are coming from very far away to see us. Only two of our patients live in Houston and the rest live all over the world, so sometimes if the interferon is not working and their disease has gotten worse it makes it more difficult for them to come halfway across the world. Plus, it is pretty expensive to come here from out of the country.

7. Would you be willing to confer with treating physicians of our patients and assist with treatment plans?

In principle, I do not want to be treating patients that I have never seen. I am uncomfortable with that situation; however, I often give general advice to physicians. I will tell them our experience with the higher doses versus the lower doses. I do not want to make a treatment plan for a patient I have never seen, but I am happy to speak with physicians and inform them of our general experience. We have done that with several physicians across the country who called us about patients who were unable to travel here. The physicians usually ended up putting their patients on interferon.

Q: How would a physician get in contact with you?

They could call or send an email. Either one would work.

8. **Do you think there will ever be a clinical trial of possible treatments with so few patients in the developed world? Do you think any type of scientific study could be done on ECD? How many patients would be needed? What would have to be in place? Could our group help make something a reality?**

I think it is going to be very difficult. I am the chair of a department that runs clinical trials, so I'm very familiar with what is needed for a clinical trial. ECD is a very rare disease. It was very fortunate that we ended up with a treatment that was successful. It is our intention to publish follow up data, but performing a clnical trial on this very rare disease would be very difficult. I know you want more research on ECD, but I do not know that it would help you any more than the published studies from the doctors. For instance, if there was a clinical trial of interferon and ECD, we would probably have been strongly discouraged from publishing the study until the trial was completed. We published the first three patients because we wanted to inform doctors and patients about our positive results. In the context of a clinical trial, in general the investigators are discouraged from reporting until the trial is complete – which is usually 15-20 patients. For ECD it would take a long time to have that much data. Clinical trials would be nice, but I think publishing experience – even on small numbers of patients – works well.

Q: What is a typical time frame for a clinical trial?

It depends on the disease. If we do a trial on lung cancer and we need 20 patients we can finish the trial in just a few months. There is a time frame for developing the trial and getting it up and running. Depending on the trial, the time frame for developing it and getting it up and running is about a year or longer. There are a lot of regulatory checks that you have to go through. We are very familiar with what is needed but it is still a time consuming process. Again, I think the enthusiasm for getting a clinical trial for ECD would not be high. That has nothing to do with me. The drug companies are unlikely to be interested in a disease that is this rare. It is just going to be hard to prove anything with a disease that is this rare. The best way may be to have people publish their experience with treatment.

Comment from patient in Canada: He has had ECD more than 20 years and has had many difficulties dealing with the political and medical system. Because of the rarity of the disease his doctors either did not want to deal with him or they did not want to work together. After traveling to see Dr. Kurzrock he has seen a change in his medical staff and they are now very willing to work together and communicate with Dr. Kurzrock about his treatment.

****

Transcription of teleconference ends, the following are personal notes taken during the teleconference

****

ECD is a very confusing disease because it can affect so many organs with different symptoms. It took her team 3 years to diagnose their initial patient. A young ophthalmologist made the first diagnosis.

What is the cost of interferon treatment? In the US, insurance will many times cover the cost of interferon, or treating physicians can get them to cover it. Carol mentioned the drug manufacturers will also help in some cases where there is a documented financial need. Dr. Kurzrock has also seen this happen. When not covered, interferon is very expensive.

What can our group do to raise awareness of ECD? Dr. Kurzrock believes the best method would be to put information on the web. We should target both patients and physicians. The site should include information about the disease and symptoms. It should include contact names for questions, including other patients and physician names. Dr. Kurzrock would be happy for us to use her name (with her having a chance to review the website, of course). We could look at other rare disease websites and get ideas from some of the successful ones. The site should include links to articles about treatments, information about how to diagnose the disease, etc.

Is Dr. Kurzrock aware of any links to RFP, myelofibrosis, cancer, etc? She is not aware of any link, but the disease may be initially misdiagnosed as another disease.

What are common symptoms that would lead Dr. Kurzrock to suspect ECD? She would suspect ECD if she saw a patient with lots of confusing problems, along with the classic ECD eye problems (bulging eyes) and diabetes insipidus. Her facility would do a biopsy to get a tissue diagnosis. It is important to realize the biopsy tissue must be sent to a center that has seen ECD before. She would recommend the biopsy be sent to MD Anderson or other places that have seen a few patients. Otherwise, if the doctor doesn't think about ECD, or hasn't seen it before, they may not be able to diagnosis

Has Dr. Kurzrock seen patients with bone involvement develop joint problems as well as issues in the long bones? She has occasionally seen this but doesn't know if the problems in the joint are a direct result of the disease of if they are secondary to the other bone problems as the body tries to compensate.

Will the bone problems correct themselves on interferon? She has seen one patient who saw tremendous improvement over 2 or 3 years. Before treatment the patient needed pain medications around the clock. With interferon the patient needs no pain medications and has became much more mobile. However, the improvement with bone involvement may be slow.

Dr. Kurzrock had another meeting she had to attend and the teleconference connection ended when she left shortly after 11 am Central time.

We were all very impressed with Dr. Kurzrock and her willingness to meet with us and share her findings with treating ECD in multiple patients. Much was learned by those in attendance and all

were grateful that she was willing to meet with the group.