

Current Concepts in the Medical Treatment of Carcinoid

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INTRODUCTION: Our next speaker is Dr. Lowell Anthony who earned his Medical Degree from Vanderbilt University in Nashville, going on to complete a residency in Internal Medicine and Fellowships in Medical Oncology, Clinical Pharmacology. Dr. Anthony is certified by the American Board of Internal Medicine, in Internal Medicine and Medical Oncology. A Fellow of the American College of Physicians, Dr. Anthony is a member of many professional societies and organizations including the American Society of Clinical Oncology, American Association for Cancer Research, American Society of Hematology and Southwest Oncology Group. He is an elected member of the Southern Society for Clinical Investigation and is an invited lecturer who has participated in numerous national and international scientific forums. Dr. Anthony serves on the editorial board of The Journal of Peptide Therapy, Index and Reviews and is Reviewer for such journals as The Journal of Nuclear Medicine, The New England Journal of Medicine, The Journal of Clinical Oncology and Cancer. Dr. Anthony is also the co-author of numerous books, chapters, journal articles, abstracts and audiovisual media. His work has been published in such professional journals as Journal of Clinical Oncology, Italian Journal of Gastroenterology, Journal of Pathology, Clinical Research, Annals of Internal Medicine and Quarterly Journal of Nuclear Medicine. I give to you, Dr. Lowell Anthony.

What I'll concentrate on today is the medical management. I don't want to rehash what you've heard this morning but certainly would be willing to take questions on that but I'll concentrate more on the medical aspect of what we do in carcinoid disease and that's not to really down play the other aspects but how we really integrate the medical component into it. Now before I get too deep into the medical component, I just want to answer the question that came up this morning of why do we do therapeutic Indium 111 pentetate therapy at Memorial Medical Center. This is the concept that Dr. Linares basically was drawing from. This is the clinical trial that was one of the reasons that I moved to New Orleans about six years ago from Nashville. I came down here to do this pilot trial and ended up having thirty-five patients that started in February of 1997 and completed the last patient accrual in December of that same year. Of that thirty-five, twenty-seven of them were gastroenteropancreatic tumor patients or were typical, well differentiated neuroendocrine patients. What we basically did in this trial was to look at how they perform from a performance level very much like that scale Dr. Frey talked to you about and also look at some biochemical parameters and looking at the CT scans and then the median survival. This trial became the critical component of extending the experience beyond this particular site. The Indium agent known as OctreoScan, we've termed the use of this drug when we use it in a higher amount and that would be 180 millicuries+ as Somatostatine which would imply therapeutic OctreoScan. The twenty-seven GEP patients, seventeen of them had what we classified as a clinical response. This would be where either the person, a caregiver or medical personnel that is separate from ourselves that would comment that these patients were doing better. These people were video taped, and if anybody wants to go back and look at that, it's available through the Foundation with Jamie Hardy. These would be people who come back. They do not have to take as many pain medications some not having to take blood thinners. Some things like, they're able to maintain their job or go back to work was observed. However, nine of them we could not really clearly differentiate that they would be improved symptomatically. The key number here is about two-thirds have symptoms improve. This is what I tell people, when we do this treatment, we're looking at a predictive factor of about 2 out of 3 are going to get improved symptoms. We've got to take people who have symptoms that we can work on so your asymptomatic patient was not a part of this initial study.

When we looked at our biochemical markers, and this is where our good friend and esteemed colleague, Dr. Tom O'Doriso was kind enough to take our samples after we batched them together. His laboratory at Ohio State analyzed them in a blinded manner. He had no idea who he was looking at. He didn't know what the samples were as it related to timing of what treatments were performed. The only thing he knew is that we wanted to measure pancreastatin. Pancreastatin is a subunit of chromogranin A. So everything you know about chromogranin A, you can apply it to pancreastatin, it's just a different antibody that's seeing a different component of the chromogranin A molecule. Of these twenty-seven subjects, twenty-three of them would have at least a greater than 50% suppression of the pancreastatin and four of them would have no change. When we look at the CT scans, these were scans done on day 60 so there would be two treatments on day 1 and then approximately on day 30 and this would be what we found at the time the scan was done. Out of the twenty-seven patients, three of them would have a significant tumor reduction that would qualify as a partial response and this would be at least a 50% decrease in the product of perpendicular tumor diameters. Now, we didn't see any complete responses. The dominant response was stable disease and that's what I tell people today. If we use Indium 111 pentetate we're more likely to see on a CT scan no change. Progressive disease was seen in three. However, nine patients had a change in tumor density and this may help understand the discrepancy between the fact that we don't see very many partial responses yet we see more clinical responses and the way we have put this together is that these changes in tumor density as measured by the Hounsfield unit, would imply that there is less tumor present to cause symptoms. Everyone wants to see survival data. This goes beyond clinical response, biochemical response, radiographic response and you would have to remember now that this group of patients had failed Octreotide acetate, or Sandostatin treatment. They had had embolization and some were previously resected. This was 1997. This is before Dr. Frey's work but they had embolizations. Interferon for many of them, the combination of Interferon and Sandostatin, everything that could be done had been done or they would not have on this clinical trial. We're looking at people that we thought were in their last six to twelve months. When we look at the median survival here, that would be between the 40 and 60, this is a cumulative percent survival on this axis, we can come over here and see that this comes at about eighteen months. We obviously don't have a control group, we don't have another twenty-seven patients that we did not treat like this however we can compare it to chemotherapy. In these two, the red line and the green line are the chemotherapy treatments that were done in the Eastern Cooperative Oncology Group in the 1970s. This is the best that cytotoxic chemotherapy has to offer. In fact it's combination chemotherapy, Cytoxan strep is the green line, 5FU Strep is the red line. We're not saving people with progressive disease with cytotoxic chemotherapy.

With that as a background, by July 1999 we had exhausted our resources at LSU to provide this therapy. We could see two out of three people improve. Novartis or other pharmaceutical companies did not have clinical trials available to people to provide access to radiolabeled somatostatin peptides. We felt somewhat obligated after a consensus meeting that was held in Los Angeles in June of 1999 where experts around the world got together. We felt obligated to be able to offer this for people in the sector of where all treatment had been given. We felt it was almost unethical not to offer it in the easiest means that we had to do was to go to the private sector where we could negotiate with insurance companies and this is basically what happens at Memorial Medical Center.

To sort of move along. Are there are questions about that did this answer the earlier question that came up with Dr. Linares? Purposely we didn't analyze the data for this conference because we look at the experience here as a treatment protocol. It's not collecting data, we don't have people sign consent forms that indicate the drug is being developed for commercial purposes. It's strictly to benefit the people who come in for the treatment and as that we're not holding people down to have to have a CT scan on day 60. We're not holding them down to have to have blood work for safety data, collected at any specific time points. That's the nature of the current procedure.

(Q) Are the treatments only available for people who are kind of on the last?

(A) No, I wouldn't really say that. We have to be careful when I think when we say that. We don't want to promote this therapy to be the end all and the cure all for carcinoid neoplasm. We want to say it has a place and that place is in conjunction with other forms of treatment. If I saw someone that I thought we could debulk with radio frequency ablation and what Dr. Frey does, I would not

promote this therapy necessarily in place. At some point when someone may not be a candidate for additional intervention, Interferon Sandostatin is no longer controlling tumor growth, it's obviously controlling the symptoms. It continues to control symptoms despite tumor progression so if Interferon has been tried, or embolization or RFA, it sort of depends on the nature of the situation but at this point we don't wait now to make someone wait to what we think is the last six to twelve months but we want to see tumor progression or symptom progression in light of other therapy.

(Q) _____.

(A) Well we've been doing this. This is not a trial. What happens here is a treatment protocol. There is not any research component. We finished the research in the group of patients accrued in 1997-1998. We continue to follow them even today. Four of the group are still alive. We're in a situation where the hospital negotiates with the insurance company to provide payment. Any other questions about therapeutic Indium?

(Q) Do you recommend Indium-111 therapy for early stage disease?

(A) Well, I think you have to define what early stage is. Most everything we see is advanced stage. I think he's probably referring to someone before, they are having a lot of weight loss or a lot of pain so it's a matter of integrating the treatment in a timely manner. We know the dose threshold for Indium 111 pentetate. We know that doses below 180 millicuries are not going to particularly be effective unless they're repeated often. So we have a good feeling of safety. We know it can be repeated. Cumulative doses between 3 and 4 curies have been done by the group in Rotterdam as well as our group here. We're starting to get some people who are between 2 and 3 curies. Dr. Krenning was the very first person who initiated this therapy in 1992. A group in Brussels gave it to someone who had an insulinoma. Their patient was subsequently written up in the Annals of the New York Academy of Sciences and after being in the hospital for nine months in Brussels with just 180 millicuries of Indium pentetate, they got this patient out of the hospital and so it was quite a success with the very first patient treated. Dr. Kernning's group finished their work somewhere around 1996, 1997 and even though they make continue it, they had accrued between 30 and 40 people between the years of 1992 to 1995, 1996 range to have an experience that this product works. That's basically the lead that I took in 1996 was to look at the Kernning experience, see that there was something to it and see that the pharmaceutical companies were really not meeting the timely aspect of providing this type of technology. In 1996 we had Indium 111 pentetate on the market. It's just a matter of knowing how to do it. What we do is order the kits, the OctreoScan kits come in from Mallinckrodt, from St. Louis. We get our Indium from Nordian in Canada. This is the old atomic energy commission of Canada. It's too bad the United States didn't privatize their old AEC. We can't do any business with Oak Ridge, they're just not user friendly. So we have to go to our Canadian friends. Our Canadian friends supply as much Indium as we want. It's just a matter of leaving the cyclotron on for a number of hours. It's not like the Yttrium. Yttrium is a harder isotope to obtain. One has to wait for decay from Strontium 90. You can't rush decay. It takes simply time. With the cyclotron, you can just leave it turned on. Any other question?

(Q) _____.

(A) Well, we would prefer to use this agent in a manner that makes sense and at the very end of my talk, I'm going to make a summary statement that kinds of reiterates some of this. You never say never because no body is the same. Our experience has been in following symptoms and I think if people have disease that is progressing and other types of treatments have either failed or not an option, then we would not necessarily wait for that person to develop end stage symptoms. I think that's probably what Dr. Linares is just reiterating that point. If there were progressive disease, no other options and, it makes sense then we would do it.

(Q)_____.

(A) As you may know, the Yttrium 90 molecule is as hard a drug to clear because these isotopes are taken back up into the body by the kidney. With the Indium molecule, with that same process, the reabsorption is what that term is called; it's not as much of a problem because the energy levels are being imparted to the kidney tissue itself. So we've not gotten into any renal insufficiency with the

experience that Dr. Linares has had or the experience that we had at LSU in our clinical trials group. The only ones that we every had any problems with were people who had renal insufficiency to start with. The doses may be different with renal insufficiency so it kind of depends on the degree of renal insufficiency. We look at that as being what called glomerular filtration rate or GFR or creatinine clearance. Once the creatinine clearance gets down to below 40 cc/minute, and this is just a volume of blood that you can look at that is cleared by the kidneys of a substance called creatinine every minute and once that gets below 40 cc, then we don't really know the dose. We really have not tested patients in that area. For the Yttrium product, they wouldn't even consider it because you would probably be going on to dialysis if you took someone like that. We've had this argument with the FDA that it's better to be alive in five years and be on dialysis than dead in one year. The FDA is so keyed in to safety; safety issues go above efficacy issues when you come down to brass tacks. This is the aspect of medicine, do no harm and in our attempts of trying to do good, we have to put do no harm right above do good so particularly when you may not know up front that you might be doing good. That's the Indium project. I would certainly be willing to talk to people more about it if there are questions. We mainly just use hydration. Yttrium requires amino acids. That's one of the big differences. We've done one patient with Indium, totally out patient. The Indium project could be moved out to outpatient. It doesn't have to be done right now. We do it inpatient because it's they way we've done it. We're very comfortable doing that but it's something that clearly could move to the outpatient arena particularly as other radio labeled drugs come along.

I'm going to shift gears a little bit and talk about how we go about making decisions for people with carcinoid. We really have to integrate what the patient's telling us. If your physician is not listening to you, you have a problem because what you're saying is as important as what anybody can see on a CT scan or what they can see on a laboratory test. You go in and you tell them, I'm flushing, I'm losing weight or I'm having pain, which registers. That should be a problem. Incorporating what a physician hears, what the patient says, what the physician sees and looking at what the biochemical markers are doing, that's one way that I like to decrease the number of scans that we do, is look at biochemical markers more often than we scan. Scans are expensive. We are dependent upon them but I don't want to scan everybody, every time I see them, I want to know what's going on but I don't want to get a scan every 3 or 4 months and so our biochemical markers really allow us to take a snap shot of what's going on. The best one to use is that one that is elevated. That's the key thing. I don't get involved with how many are elevated as it is which one is the best marker to follow. I want a marker that's going to reflect the extent of disease and that's going to be relatively easy to measure. That follows pretty much with a 24 hour urine for 5HIAA or the plasma chromogranin A. There are strengths and weaknesses to each one of those but I generally like to get one of those markers and don't get too confused with measuring multiple markers because what do you do when one marker has gone up and another marker has gone down. It becomes confusing. What is helpful is to match what markers are doing. The changes in markers with what the person is saying and then looking at what an abdominal CT scan or an MRI or OctreoScan might be telling us. If it doesn't make sense, if there is a discoordinancy, if the patient's losing weight and the CT scan says no change and the markers are going up then that tells me that our CT scan, just the technique is not sensitive enough to pick up the changes. It's like a CT scan is not a CT scan, it depends on the protocol that used to obtain that CT scan. For carcinoid patients, I feel fairly strong that the protocol ought to be fairly detailed. It should not be a CT scan that would be obtained for somebody who did not have liver involvement. It's helpful in my experience to have the radiologist know that there is something in the liver and if they can know that, then the windows can be changed and the settings can be altered so that the disease in the liver can be seen readily and descriptions made according to what the prior scan is. I frequently will order an abdominal scan with and without IV contrast with and without liver windows and please compare to the last scan. Usually that comparison of the last scan is usually just a marker for everyone to know that there is a prior scan or not. That's the nature of trying to work in bringing together all of the data, bringing together what the critical aspects to make decisions and then what are those decisions. The decisions have changed over time and I hope they continue to change. We've got to get better at what we do. We've got to start treatment and it depends we can argue when to start treatment and we can argue what to start with. In general, when symptoms are present, we need to start treatment. When symptoms are not present, we can debate it. Once a treatment decision has been made, then it comes down to saying how good a job are we doing, is the treatment working? There's a critical balance that the treatment should not exceed what the disease should be doing. That is the critical aspects of determining what decisions ought to be made is knowing what that disease should be doing at that particular stage and

understanding what the drug therapy might also be doing. Once the treatment has been instituted, looking at signs and symptoms, repeating the imaging, laboratory and adjusting monitored therapy. Right there you've got it if you can put together all that on one sheet, then that's the critical aspects of making decisions.

I'm going to reflect back for a few moments to the Father of Carcinoidology, Dr. Charles Mortel and I think his writings and his research will live for many, many, many years. Dr. Mortel was known to classify carcinoid to tell people that carcinoid is cancer in slow motion. I'm a firm believer that carcinoids when treated with Octreotide is cancer in an even slower motion. I didn't say no motion but I said slower motion. The data is overwhelming. Even though it's a bit like tobacco and cigarettes and lung cancer. We're not going to totally get to a point where we can do the right study to prove that Octreotide is an anti-tumor agent because we're not going to have a control group, at least in carcinoid we won't. We have to look at what our data is telling us and what does this mean. I've thought a lot about what Dr. Mortel has said and dissecting this out. What are the messages, what's hidden in between the lines of what this observation is. We know that carcinoid is cancer. We know cancer is a disease of the DNA. The fact that Dr. Mortel said it was cancer, then we have invasiveness, we have metastasis, we have the behavior like neoplastic cells. We know that there's going to be molecular events occurring. We've got to be smart enough to figure out that aspect of it.

The next thing that this tells us is that it's not the fact that these cells are growing, dividing every ninety days as some tumors might do. This is where the cells are slowly dividing and are accumulating and we need to have the cells fall off like the tail of a tadpole. We've got to figure out how to be thinking along the ideas of getting rid of these cells that are accumulating. In the process, these accumulating cells are causing a lot of harm by releasing hormonal products and that's the unique aspect that brings us together as a group today. How do we marry this concept of cells accumulating is a greater problem than the cells dividing. We process that into, let's think about having drugs that would be telling the tadpole tail to fall off and that term is called apoptosis rather than mitosis. Not to say mitosis is not important but our agents are not killing cells that are not dividing then we probably aren't doing very much in controlling this disease.

What are the stumbling blocks? We don't have any good test to pick up this disease early. We have really no screening tests. This is a big problem for other cancers. There's a lot of interest in a new marker for ovarian cancer; it's going to take more time for it to be delineated. Pancreatic cancer is one that frequently presents with metastatic disease. Chromogranin A is not a sensitive marker and 5HIAA acetic acid is not such a marker either. Once those markers are up, you've got metastatic disease. Carcinoids are rare disease. We have estimated somewhere maybe 3,000 new cases a year, cumulative may be 10 to 20,000 people are alive in the United States with it. May be equal numbers or greater in Europe. There are no cell lines that are really practical. There are some cell lines that have been developed from a special kind of rat, a little mouse in Africa called the mastomy, but that is a highly specialized cell line that does not really reflect human carcinoid disease but it does give insight into enterochromaffin like cell activity so there are some useful models to study neuroendocrine cells but have not been useful either in cell culture because these cells don't grow very fast and if you don't have a tumor that grows very fast then your animals may outlive the tumor in that regard. It's very difficult to have animal models. The times that I've tried to take carcinoid cells and pass them through sieves and disperse them and put them into animals; Courtney Townsend did this work for me. I would send them down from Vanderbilt, we probably did a half-dozen samples like that and after about two years, he'd call me up and say, Yep we got one to grow, two years later. It's a little bit frustrating. We have no easy access to a gene bank set up that we can look at molecular characteristics, either the tumor cell or the genetic endowment of the person.

The other thing is that most of the drugs that we use in Oncology are ones that are going after the DNA synthesis. This is the taxanes, anthracyclines and drugs that are used for tumors that have faster half-lives.

As we look through sort of the medical aspects of the progress in the twentieth century, we have to really go back and say that the 5HIAA that Dr. Mortel at the NIH at that time that was discovered and he became interested in flushing and carcinoid, but the 5HIAA becomes a critical linker because in the 50s and after that we didn't have CT scans and OctreoScans and bone scans and stuff that we

could classify people in the same group. When the 5HIAA was elevated, we could look back on that and know that those patients had metastatic disease and 9 out of 10 of them will have disease in their liver. We start to get some homogeneity in our experience when this becomes a key elevated marker.

What happens in the 60s and 70s; this is the decade, the years of what called MOPP. This was the time when lymphomas were being melted and were being cured with MOPP regimen, which basically was cytotoxic agents and steroids. This is where 5FU was found to be the most active drug in colorectal cancer and subsequently it has found to be the most active drug in carcinoid. All the work that went in for twenty years after 5FU was discovered in 1957 is summarized by that statement. We can give 5FU alone; we can give it in combination. We don't help people anymore when we give it in combination than we give it alone. So, if we're going to look towards the 1960s and 1970s, then we have to look at 5FU as being the biggest advance out of that. In the 1960s there was a drug called Cyproheptadine or Periactin and this product is effective in controlling diarrhea. You have to be a little bit careful, it can cause some disturbed mental status changes. I recall one of my patients at Vanderbilt went into the call room and woke up the intern in the middle of the night. It was a patient I had on Periactin and he basically was acting like he had Alzheimer's, he didn't know where he was. We stopped the Periactin and he became normal again. I have a big respect for what Periactin can do for people.

In the 1970s and 1980s, this is where we really start making some progress. In the late 1970s, around 1977, 1978, Dr. Oberg's group in Sweden made the observation that Interferon as a class can control the flushing, can lower the 5HIAA acetic acid and this was some of the early advances simply because of the Finnish, Red Cross was based in Helsinki. Dr. Oberg's group had access to this. They had enough patients in one center to study because of the logistics of the Swedish Medical System. What Dr. Oberg has taught me is that it's the alpha 2 B Interferon or the Intron A that is the best to use and this is where you don't have to worry blocking antibodies as opposed to the 2 A product also known as Roferon. What's happened in the Interferon world in the last few years is now we what are called pegylated Interferon. This is simply another form that doesn't have to be administered on a daily basis. My good friend Joe Pisegna at UCLA has done some nice work with combination Sandostatin and pegylated Interferon. Also the group in Germany is very active in combining these drugs. My bias is to start off with OctreoTide and add the Interferon as a supplement later because of the toxicities of OctreoTide versus Sandostatin or Sandostatin, OctreoTide versus the Interferon are quite significant.

The next major change, the next major advance was in the early 1980s when peptide chemists got together at a meeting and they came up with a concept of stabilizing what is normal or native Somatostatin to stabilize using this product so it becomes a therapeutic agent. The genius from this conference was that you could substitute and put these two L forms of amino as these D forms amino acids in two positions and change the ending to an alcohol ending and stabilize the molecules to plasma degradation. This is what happened with Octreotide use. This is Dr. Mortel's data. He published ninety-one patients and this is his early experience published in 1971 on what could be done prior to that. We can look at that. All of these patients had elevated 5HIAs. We know they have metastatic carcinoid. There is not another neoplasm or condition in medicine that has an elevated 5HIAA. We are comparing apples to apples here, the only difference we've got about a twenty-five year difference in terms of time. People could argue that we're detecting disease earlier because we got CT scans; where all these people have elevated 5HIAs today, so it doesn't really matter that we're detecting them earlier, they still have advanced disease. What we can say is after the introduction of Octreotide; the median survival here goes from around two years out now to around between six and seven years. You could also argue, well we've got embolization and we've got hepatic surgery and we've got all these other things going on. Well yes, that's great but we do know is that patients do better with stage 4 disease after 1986 than they did prior to 1986, a critical year in medical history.

Where are we today? I've already shown you the Indium work. The Yttrium work is in progress. I really can't report to you today on what has been done with Yttrium 90 other than to say doses have been figured out that are safe. We administer approximately 120 millicuries of this agent spaced out six weeks or so and do this three times. This is a protocol that Novartis is developing and is being done across the country and you all are well aware of it. Dr. Kvols in Tampa has the greatest

experience in terms of what feedback; he tells me that symptoms are improved. That's pretty much what I've heard from him. We made that loud and clear in 1999 in L.A. that with Indium, symptoms are improved. Also, a group in Austria has used Lanreotide. This molecule has a tyrosine present and it can be iodinated and can be used for treatment in that regard. The treatment there, the I-131 product doesn't have a major sponsor behind it so it's going to be somewhat delayed if ever developed.

What to expect? Here I want to be a little futuristic. I guess that's one of the reasons you all came today is, where are we headed in this area. Novartis is working very diligently on looking at somatostatin analogs that have a broader spectrum of binding. My understanding is that this molecule will be going into human testing fairly soon. It's going to be seeing four of the five Somatostatin receptors. The Octreotide sees one really good, sees two somewhat good, sees three a little bit. I'm not really sure what it's going to mean by having a broader receptor inhibition. We'll have to look at this in an objective way and see if we buy anything with these added receptors.

There is a group here in New Orleans. There's actually two groups here in New Orleans that are working diligently on conjugating cytotoxic drugs to the Somatostatin molecule. This would be the same concept but instead of putting Indium 111 or Yttrium 90 or Lutetium 177, that's the most recent isotope that people are talking about, Lutetium 177. It's a lower energy beta so it's safer to the kidneys. Instead of using those radio labels, you know, get away from radiation potential complications or a cumulative dose once it gets to a certain point, then to get a cytotoxic agent incorporated into the cell so than an apoptotic mechanism can be activated by one of these drugs, then we've got potentially a product that's safe. My understanding is that in the animal models, the cytotoxic conjugants are very well tolerated by the animals. I think that's really some interesting things that will come along. I've been told that some clinical trials with these drugs may start some time this year.

Tyrosine kinase inhibitors. We're all looking for the Gleevec. If that word means anything to you. This is a drug that was approved in May of last year for CML, chronic myelogenous leukemia. Just a month or so ago it was approved for gastrointestinal stromal tumor. GI stromal tumor called GIST is a sarcoma of the intestines. There was nothing for this group of patients prior to this drug. This is somewhat of a home run drug. We're not used to making big steps in Oncology. Platinum was a big step in 1970s in germ cell malignancies and MOPP was it for lymphomas. Those are rare and few and far between. But Gleevec is what is classified as a tyrosine kinase inhibitor. It removes or blocks the molecular pathway that is responsible for telling the cells to grow. CML expresses the Philadelphia chromosome that is a molecular target for Gleevec. So this is very exciting.

Does this play a role in carcinoid? Exciting question. I've tested a half dozen tissues so far for CD 117 or a special tyrosine kinase and I haven't found it yet. Does that mean there won't be a place for it? No. It's not a home run. It's not a home run like GI stromal tumors. It's not a home run like CML.

Angiogenesis inhibitors. Endostatin, potentially an exciting product. Again a product that would mimic insulin for a diabetic. This is something that we can continue on a chronic basis and control the disease. So active trials are going on in Endostatin with some success as it relates to controlling flushing. There is at least one person here in the audience on such a trial. Anti veg F monoclonal antibodies. Drugs being tested in a number of different neoplastic conditions. We know carcinoid is a highly angiogenic tumor, very vasoactive so this would be of potential value. I am unaware of any clinical trials going on. I don't see down the road why this would not be the situation. There are also small molecules that attack Veg F. Novartis has one that will be going into clinical trials sometime later this year if my understanding is. This one would obviously be by IV. Novartis' drug is looked at as a potential oral formation.

Thalidomide. It wasn't very long ago that thalidomide came to us and it was something that we wanted to put most people on when we had no other choices because it's oral, and not metabolized by the liver. It's strictly cleared by the kidneys. Thalidomide certainly can control the diarrhea. There is one study going on in Albuquerque looking at thalidomide in carcinoid. I've used it strictly really for side effect of controlling diarrhea. I've not done any formal studies. I've put a number of carcinoid patients on it. It's not anything that I see that's going to lower the 5HIAA. A lot of sleepiness and other thing. I use it more as a supportive care drug than I do as an anti-tumor drug.

The bisphosphonates. This is an exciting area. There is a class of drugs that basically homes right to the bone, when these drugs are given intravenously. When this drug is taken up into the body it basically goes to the bone and over time it is released but where the bones are being attacked by the tumor, there's a cell called an osteoclast. These bisphosphonates target the osteoclast. They block the resorption of bone, stabilize the bone and the disease that has been studied to date which would be breast cancer, prostate cancer, myeloma among others; the incidence of fractures and pain have been substantially altered. Just a week or so ago, the FDA approved this drug here, Zoledronate or Zometa for bony metastases. That's a broad, broad approval. Not just bony metastases from breast cancer but bony metastases. So patients that I see with carcinoid, I put a number of them on this class of drugs. We have to look at it for stabilizing the bones. We have to think of fracture. We also have to think later on of complications.

Pamidronate is the drug that was available before Zoledronate and it's one that we have some experience with as well.

Epidermal growth factors. Gee, everywhere you turn everybody is talking about epidermal growth factor. To me it's somewhat nostalgic because I can from an institution that EGF was discovered by Stan Cohen. Stan Cohen was a personal friend of mine. I know Stan Cohen. He won the Nobel Prize for this. As I look at EGF inhibitors, there's a good story here. C225 is one that been in the news a lot lately. There's been a lot of discussion within the last three months between M-Imclone and Bristol-Myers because the FDA didn't fast track this drug. In fact they totally rejected what data that they submitted and Bristol-Myers invested a billion dollars was a little upset. You may have seen the slide that Dr. Woltering put up earlier. These carcinoids make growth factors. There is EGF-1 that we can potentially target so you can kind of see where we're head down the road. We're going to be taking carcinoid specimens and having out pathologists stain them for different not only peptide receptors potentially but for other molecular events, molecular targets such CD-117 that the Gleevec or EGF that's some of these. Herceptin is HER-2Neu. It is a epidermal type growth factor that's expressed in breast cancer. The product is on the market. About 15% of breast cancer patients may benefit from this. Iressa, is a compound that's being developed that blocks EGF, Astra Zeneca is developing this oral product for lung cancer and other malignancies that express the EGF receptor.

New agents, Epothilones, is a group of a class of drugs that would be classed more as cytotoxics but are being tested now in colorectal and other cancers including even carcinoids. The Epothilones are a bit like the taxanes. They stabilize the tubulin polymers so that these cells can't divide. What's interesting about the Epothilones is that they may also trigger apoptosis. This would be some area to stay tuned to but this would be chemotherapy-like.

Finally thymidylate synthase inhibitors. If we look at 5-FU as being an active agent, then some of the newer generation of 5-Fluorouracil might play a role down the road. These would be drugs that are not sensitive to the resistance mechanisms that 5-FU is. This particular agent, Thymites is being developed in hepatocellular cancer and in some other malignancies and it is a lipophilic drug which means that it will go into the cell without a carrier and the mechanism of getting that drug out of the cell, what happens with 5-FU is not active with Thymite so that we're not looking at the multi-drug resistance characteristics as being a rate limiting step.

Other. This is sort of like where you could just look at drugs that are out there. There are some products that are being used for rejection, some monoclonal antibodies that are being used in kidney transplant patients and liver transplant patients that might play a role in controlling neoplasm. Drugs that are being used in arthritis could also be potentially used in carcinoid and one of them particularly could be and this is one that looks at TGF beta. There is a monoclonal that could target this particular product that might prevent some of the carcinoid heart disease that might occur.

In order to start summarizing up, staging assessment; physical exam, a spiral hyperdynamic CT or MR, nuclear med OctreoScan, initiate therapy, Somatostatin analogs first, In the early 1990s, Dr. Oberg was very insistent that you start Interferons first. He eventually converted to seeing that Somatostatin analogs should be used before the alpha Interferon. Titrate therapy, control flushing, control side effects, Octreotide titration in 50 mcg increments, Interferon three to five million units three to five x a week, pegylated Interferon that will be obviously a little different. The additional

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cyto-reductive measures as needed, debulking, RFA, embolization and then consider investigative approaches. What is it going to take to make progress? Are we in a rut? Can we just not go anywhere in terms of seeing where to go? More and more work is being done to delineate the molecular characteristics. The MEN-1 gene has been described and that is, even though it's not necessarily related to carcinoid, it's another type of neuroendocrine tumor that's hereditary. Looking at DNA, RNA protein, more and more people are doing this with the HER-2Neu. I reviewed a paper recently that looked at this marker in a subtype of neuroendocrine tumors called gastrinomas. It's going to be a small subset from what it looks like. It's not going to be a home run like the CD-117 was for the GIST. Growth factor identification inhibition; this is where the EGF or the TGF beta, we can look at these pathways and block them and then we may be making progress. Developing new drugs that take advantage of looking for these molecular defects and then again I want to emphasize the fact that we need drugs just like what happens in the tadpole. We've got to get that tail off the tadpole.

What can you do as patients, as caregivers? Work with your healthcare professional. Report the signs and symptoms that you're experiencing. When it seems reasonable for you, go into a clinical trial. I think this is something that allows us to compare apples to apples for the most part and to make advances in this area. Keep educated as these seminars; obviously the support groups on the Internet keep you informed. I think the newsletters that Jean puts out are wonderful and I think the Internet has really made us come together and has made a difference I think in the management of this disease. To summarize it all, I think we can clearly say that not all neuroendocrine tumors are created equal and this is where going back to Dr. Linares, all treatments are not equal. We really can't be dogmatic and say yes we will, no we won't on doing anything in a cookbook type manner. To quote Steve Vatcherie, the future is not what it used to be but also you've noticed that I have done a little bit of predicting. I'll just end right there and I'd be certainly happy to take any comments or questions.

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