Carcinoid Tumors and the Carcinoid Syndrome: What's new in the therapeutic pipeline

Presented by

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Dianne Comstock:

Our first speaker of the day is Dr. Larry Kvols who is accompanied by his two wonderful nurses – Valerie Bennett and Nancy Gardner. You will be hearing from them later on today. Dr. Kvols graduated from Baylor College of Medicine, Houston, Texas with high honors.

Dr. Kvols has been a consultant at Mayo Clinic in Rochester, Minnesota, and a Professor at Mayo Medical School. Director and Chief Executive Officer of Cancer Research and Treatment Center at the University of Albuquerque, New Mexico. He is very well known in the international lecture circuit. He is the author of numerous original research articles and scholarly medical articles and it is timely to mention that Dr. Kvols has brought into two handouts. One from a chapter that he has authored from a medical text published by W.B. Saunder's, which is included now. Everybody should have a copy of that and we thank you very much Dr. Kvols for doing that.

Currently, Dr. Kvols is a professor of medicine in the GI Tumor Program at H. Lee Moffitt Cancer Center in Tampa. It has been my privilege to be one of his patients since 1999. Today, Dr. Kvols will discuss carcinoid tumors and the carcinoid syndrome, and tell us what's new in the therapeutic pipeline. Please welcome Dr. Larry Kvols.

Dr. Kvols:

"Good morning! It is quite a privilege to be here and see so many people that I have known for five, ten, in some cases fifteen or more years. The number of people who are here this morning astounds me. I thought that I might see 30 or 40 people when Dianne first started talking about this meeting and she told me yesterday that there were some 255 people who had registered for this seminar. She had a fun idea of putting the map out there in the hallway with pins on it from where people have originated in this country and we had to draw a little addition because of this nice lady from Puerto Rico. I think that there was nobody here from Hawaii or Alaska, but we have people from all over the U.S. So…welcome! I think that you're in for an enjoyable and informative day.

It is an honor for me to have Dr. Tom O'Dorisio on the program with me. I was just reflecting, Tom, I think it has been eighteen years since you first invited me to a symposium on carcinoid tumors out in sunny southern California. We were both just getting our feet wet with first use of Sandostatin in humans Tom organized a symposium and invited me to speak and I think at that time I had experience in all of nine patients who had received Sandostatin for their carcinoid tumors. When you try a new drug and it works so dramatically it generates tremendous excitement not only for your patients, but for you as an investigator and for the scientific community at large and there was just phenomenal excitement back in the mid 80's when this drug first became available for use in humans. In fact, the first humans were treated in 1984 and the FDA approved the drug in 1988 because of the remarkable safety record and the remarkable effectiveness of it. That was before the era of AIDS and it was the fastest that the FDA had ever approved any drug from first use in humans until it was commercially available. Since them, there have been a number of exciting

developments in this somatostatin field. Many of you know that Sandostatin is a synthetic version of somatostatin and the whole somatostatin field has just burgeoned over the last twenty years and we now have not only the immediate acting form of Sandostatin, but a long-acting release form of Sandostatin that many of you are on. We have a somatostatin compound that has a radioisotope attached to it that we use to diagnose and determine the extent of spread of carcinoid tumors. This is called Octreoscan. We have new analogs of somatostatin that have radioisotopes attached to them that we can use as treatment for these tumors. So, an exciting group of advances in a period of twenty years and I think we are just really beginning to scratch the surface of this field in terms of what is still to come.

We are going to talk today about so-called neuroendocrine tumors. Many of you have heard that term and neuroendocrine tumors represent a group of different tumors that all have in common the fact that they originate in the developing embryo from the primitive neural crest and during embryonic development these cells migrate to various parts of the body including the pituitary, the thyroid, and the islet cells in the pancreas. Some of these neural crest cells end up in the lung, and some of them end up in the gastrointestinal tract. When these various cells become malignant then they give rise to tumors that are called islet cell adenomas or carcinomas when they arise in the pancreas; medullary carcinoma of the thyroid when they arise in the C cells of the thyroid; and when these same neural crest cells that migrate to the GI tract become malignant they give rise to the carcinoid tumor.

This is a biopsy from a small intestine, and this is the wall of the intestine and this is the lumen where the food passes through and lining the small intestine is the mucosa. This is an immunohistochemical stain, meaning it’s a stain that uses an antigen-antibody reaction and it looks for serotonin. These are the neural crest cells, which in the GI tract are called Kulchitsky cells, and they stain red because these two cells have serotonin in them. These are the cells which when they become malignant give rise to carcinoid tumors.

Carcinoid tumors are not as uncommon as you might think. In a huge series of autopsies at the Mayo Clinic over several decades, Dr. Moertel observed that one out of every 150 patients who had an autopsy was found to have a carcinoid tumor in the small intestine. Most of these were small, asymptomatic, and had never given rise to any clinical symptoms, but they are not uncommon and one of the questions that I always ask myself is why do one out of 150 patients who die and have an autopsy for whatever reason have a carcinoid tumor and most of them have never had symptoms from it whereas some patients will have these tumors that do spread to lymph nodes, do spread to the liver and do give rise to the carcinoid syndrome. It remains a mystery. We do not know what causes carcinoid tumors. Why some people have them, live with them for decades and never have had trouble from them remains a real conundrum.

Carcinoid tumors in the appendix occur in about one out of 300 patients who undergo appendectomy. They are usually quite small and when they are less than 2 centimeters in size surgery is usually curative. In a large series of proctoscopies in which the lower portion of the intestinal tract is examined with the rigid scope, rectal carcinoids were found in about one out of every 2,500 proctoscopic examinations. So, they are most common in the small intestine and within the small intestine they can give rise to mechanical problems may be way out of proportion to their actual size. Some of you in the audience will be able to relate to this. Many people before they are diagnosed will have symptoms of intermittent abdominal pain, bloating, distention, sometimes diarrhea and this may come and go for months or years before the diagnosis is made.

This is a CT scan from a patient who had a tumor that was just about 1.5 centimeters in size. That is about between three-quarters and half of an inch. It was causing some kinking and narrowing of the intestine in the same way that you might kink a garden hose to move your sprinkler without getting wet. The tumor, although it is quit small, has spread to the lymph nodes here in the abdomen and it is causing this sunburst appearance which is scar tissue. There is just a small tumor in here that it is causing a lot of scar tissue formation.

These are some lymph nodes in the mesentery. The mesentery is the connective tissue that surrounds the small intestine. So let me show you what we have got here. When this tumor was removed, here is that lump and this is all that sunburst appearance. That is the scar tissue and see

how it is kinking and narrowing the intestine and that can make it difficult for food to get by and that is what can cause the bloating, distention and intermittent pain. This all happened because of a tumor that was only 1.5 centimeters in size. So there are mechanical problems way out of proportion to the size of the tumor. We have a very low threshold for exploring patients when they have symptoms that suggest intermittent partial small bowel obstruction particularly if we can identify an area of narrowing because we can often improve symptoms by resecting that area of small intestine. Sometimes we cannot remove the scar tissue in the mesentery because it is densely adherent to other tissues and if we tried to totally remove it, we would have to resect huge amounts of small bowel, but we attempt to do bypasses when it is not possible to do total removal of the small intestinal tumors.

Now, there are several different parts to the small intestine. It starts right after the stomach and that part of the small intestine is known as the duodenum. The next part is the jejunum and the last part is called the ileum and there is an upper part of the ileum and a lower part of the ileum. Carcinoid tumors are uncommon in the duodenum and the jejunum. They are most common in the distal ileum and most common of all in that terminal two feet of small intestine right before it empties into the large intestine. A huge percentage of our patients who have small bowel carcinoids actually have their carcinoids arise in this distal ileum and that’s why when surgery is done to resect this and you have to remove the lymph nodes you end up removing part of the small bowel and a part of the large bowel called the right colon.

Now, in this series of 183 patients who had carcinoid tumors of the small bowel, 46 out of 183 had multicentric primaries. That means they had more than one carcinoid tumor. Sometimes three or four. I have seen as many as 110 individual carcinoid tumors in the terminal two feet of the small bowel. The take home message for the surgeons here is that because of this multicentricity it is imperative that he or she meticulously feel the entire small intestine once they have identified one tumor in the small intestine to make certain that aren’t others in the remaining portions of the intestine.

We have been talking a lot about small bowel carcinoids because that is, in my practice, and in the practice of people who specialize in this, the most common site of the primary tumor. The carcinoid tumors can also arise in the airways and these are so called bronchial carcinoids. I have already told you that they can arise in the rectum. They can arise in some very unusual locations like the voice box or the ovary. The most common ones that we see are of intestinal origin or bronchial origin. I have shown you an example of a tumor that was 1.5 centimeters in size. This looks at a number of patients and correlates the incidence of metastatic disease, that is the spread of the carcinoid tumor cells from one site to another, and the size of the primary tumor. This can be helpful when I discuss the potential for future recurrence with patients. When these tumors are very tiny, less than 0.5 of a centimeter, they virtually never recur. Most of these were found incidentally. Even when they are nearly a 1-centimeter in size, only 15% will ultimately recur. Once they get to be between 1 and 1.4 centimeters in size, 60% of the patients will have a recurrence of disease or have disease in the lymph node at the time of diagnosis. Some of these patients who have lymph node disease at the time of diagnosis and have that removed are cured. When the tumors approach 2 centimeters, 84% of them have already spread to lymph nodes or liver and when they are over 2 centimeters in size, that is approaching an inch, 95% of them will be associated with metastatic disease. So the larger the tumor becomes the more likely it is to spread to lymph nodes, liver or other sites.

Many of you in the audience will be able to relate to this and I think it is a very interesting bit of information. This looks at the duration of symptoms prior to diagnosis. Last night, they were handing out buttons. What does it say? If you don’t suspect it, you can’t detect it. I don’t know who came up with that, but it’s really true. I am sure Tom can relate similar stories, but many of the patients that I see have been complaining of belly pain, flushing, or diarrhea before they are diagnosed and, in fact, in this series of 56 patients the average duration of symptoms before diagnosis was four years. But look, 13% of patients had symptoms more than ten years, 20% of patients have symptoms for five to ten years. The range is phenomenal. One patient had symptoms for just two weeks before he was diagnosed, but this patient had symptoms for 21 years before he was diagnosed. I will show you a picture later of a young man who was flushing back when he was in high school and he wasn’t diagnosed for about 18 or 20 years. So, how many of you can relate to this slide?

This slide is difficult to see from the back, but I just wanted to demonstrate that tryptophane which is an amino-acid that we get in our foods through various proteins, is the precursor or the building block for something called serotonin and serotonin is the substance that carcinoid tumors can produce in excess. When serotonin is broken down in the body, the end product is 5-hydroxyindoleacetic acid or it is abbreviated 5-HIAA. Any carcinoid patient in the audience will be familiar with this because you have collected 24 hour urines so that we can measure the 5-HIAA. Nancy Gardner will be speaking more about this and other biochemical markers in her presentation this afternoon, but we find 5-HIAA to be one of the most valuable markers for following the pace of the disease and carcinoid tumors. Some of you have serotonin levels measured and they can be helpful in some situations, but I find that they can fluctuate much more significantly from hour to hour and day to day and so this 24 hour urine collection gives you a much better idea of what is going on over a 24 hour period of time. The value is highly reproducible from week to week in individual patients. Amino enzymes in the liver rapidly break down serotonin and other compounds that these tumors make. So, if you have a tumor in the intestine or in the lymph nodes, the drainage from that tumor goes through the liver and, boom, the liver breaks down the serotonin into an inactive substance. You don't see the malignant carcinoid syndrome unless you have hepatic metastases. That is, the carcinoid tumor has spread to the liver or in very rare instances when the primary tumor has direct access the systemic circulation. An example of that might be a person who has a primary carcinoid arising in the ovary. The blood drainage from the ovary does not go through the liver. It goes directly into the systemic circulation. So with ovarian carcinoids, for example, you don't have to have liver metastases in order to have the carcinoid syndrome. But 99% of the time if the patient has flushing, diarrhea, wheezing or carcinoid heart disease they have it because the carcinoid tumor is in the liver. The tumor cells are producing serotonin, which causes these symptoms.
What is the carcinoid syndrome?

Four key features characterize it. flushing is primarily a phenomenon that causes facial redness, sometimes neck and upper chest. It is very unusual for it to affect the entire body. Sometimes it will just affect the cheeks. Sometimes it will affect the entire face including the ears and the intensity of the flush may vary depending upon the precipitating factor. Common precipitating factors for flushing are stress, eating, and alcohol. How many of you have learned to avoid alcohol altogether because you know it causes flushing and makes you very uncomfortable? (Show of hands). I had an interesting patient when I was at the Mayo Clinic about ten years ago who was diagnosed with carcinoid just before Easter and we were doing diagnostic testing and he had not yet been started on Sandostatin. He was brought up as a Catholic, but had not been to mass for about twenty years and he decided now that he had this new challenge in his life, this disease called carcinoid, that he would go to mass that Easter Sunday. He took communion and he took a little sip of wine and by the time he got back to his pew he was dizzy, intensely flushed, and passed out. They had to call the ambulance and he was taken to the emergency room. He was so sensitive to alcohol that he had developed a carcinoid crisis, which is associated with very low blood pressure and he passed out. Well, he came back and told me that he felt the hand of God was upon him that day, and he never missed mass after that. He thought he got a message from above.

Some people are so sensitive to alcohol that they can't even use over-the-counter medications like Vicks cough syrup or liquid Imodium because these preparations have alcohol in them. (Question about cooking with alcohol. I think that when you use wine in cooking that you cook off the alcohol, but there is probably some left. *see footnote at end of lecture) Some people are exquisitely sensitive. Some people can't use Listerine or Scope because these have alcohol in them and they will have trouble from that. Other people have learned that if they have a sip of wine they will flush, but they can go on and finish their glass of wine or have a couple sips of beer, and they'll flush and then they can drink the rest of it without problems. The second major feature of the carcinoid syndrome is diarrhea. The serotonin causes thickening of the heart valves, particularly on the right side of the valve - the tricuspid and the pulmonic valves and this can lead to the third feature of the carcinoid syndrome, CHF, congestive heart failure.

Another compound that these tumors often secrete is substance P and it can cause spasm of the muscles lining the airways and give rise to asthma. In a group of 91 patients, analysis of how they came to clinical attention revealed that three-quarters of patients came to attention because of

diarrhea. Two-thirds came to attention because of flushing. You can have severe diarrhea with virtually no flushing. You can have severe flushing with trivial diarrhea, but most commonly patients will have both flushing and diarrhea. About 20% of patients first come to medical attention because of the thickening of the heart valves on the right side of the heart and have symptoms of congestive heart failure. Less than 10% come to attention because of asthmatic type symptoms.

There are a variety of different substances that are produced by these tumors. I have mentioned serotonin and I have mentioned substance P. Sometimes bronchial carcinoids lack an enzyme that changes 5-hydroxytryptophan into serotonin so they may only secrete the precursor, 5-HTP. Adenocorticotrophic hormone (ACTH) is a substance that stimulates the adrenal glands to produce cortisol and when the carcinoid tumors are producing excess ACTH the patients will have very high levels of cortisol and develop a disease called Cushing's syndrome.

Sometimes, stomach carcinoids produce histamine and we look for evidence of that with a 24-hour urine collection and measure something called 5-MIAA. Sometimes carcinoid tumors also secrete catecholamines. These are the substances that are secreted ordinarily by the central part of the adrenal gland and these are substances that are involved in the so-called "flight or fright" mechanism. If you are almost in an accident, you end up afterwards with your heart racing because catecholamines have been released from the adrenal gland. Well, sometimes we find after a procedure such as embolization that the patients will have high blood pressure instead of low blood pressure and that is often due to release of these catecholamines. When excess gastrin is produced you get stomach ulcers. When excess insulin is produced, and these are pretty uncommon, you get low blood sugar.

So, many patients want to know "how long do I have to live, doc?" I have had symptoms for years. How long do I have to live? This is always a very, very difficult question for me to answer. This is information primarily from the 50's, 60's and 70's. So, this is of historical interest and people are living much longer now, but this slide depicts the natural history before we had Sandostatin, before we had hepatic artery embolization, before we had any of the new therapies that we have today. This slide shows the duration of disease from first onset of symptoms until death due to metastatic disease median duration is nine years, but look at this range from 1< to 45 years. You can see why it is very difficult in an individual patient to answer that question. How long do I have to live? A third of patients will live from 10 to 20 years, 15% will live more than 20 years. Yes, some people in this series died within the first five years, but we don't really have the ability to predict who is going to fall in which of these categories and there are some of you in the audience who have been living more than 20 years already, with your disease.

This is the young man I mentioned who was flushing back in high school. His ninth grade high school picture did not show any flushing, but by the time he was a junior and again as a senior he had flushing affecting the cheeks and he was not diagnosed for the next 18 years. He is 34 years old now and you can see the flushing affecting the cheeks and around the mouth. I am just going to show you a few examples of carcinoid flushes. When this lady flushed, she never had flushing around the mouth. It was always just flushing of the cheeks. This gentleman had flushing not only affecting the cheeks, but when he flushed he also developed red ears and some redness in his neck.

One of the things that differentiates carcinoid flushing from hot flashes that are seen just before menopause (perimenopause) or after menopause is the fact that the patients become visibly red. In the black population where we can't see the redness the manifestation may be primarily injection of the whites of the eyes, they become red or they have excess tearing. In the Caucasian population, you can see the flushing associated with carcinoid. It is not just a sensation of warmth. The patients become visibly red. This gentleman has sort of a bluish hue because he has been flushing for so many years before he was diagnosed that there was sluggish blood flow in the dilated veins of his cheeks and that's why there is a little bit bluish tint.

This was a farmer from North Dakota whose friends when they gathered at the corner coffee shop for breakfast on Friday mornings, all thought that he was an alcoholic because he had a red nose. So they thought he was hitting the bottle on the side and never drank in public. But, in fact, he avoided alcohol for more than 20 years because it caused intense flushing and his red nose was due to carcinoid, not from being an alcoholic.

I would like to talk for just a moment about carcinoid heart disease. Because patients are living much longer now than they did in decades gone by we are seeing more carcinoid heart disease. Twenty years ago, we could do very little for this disease, but now we are increasingly offering patients whose carcinoid syndrome (flushing and diarrhea) we have under control, the opportunity to undergo open heart surgery and replace these diseased valves. This is the appearance of a normal valve in the heart. These are delicate little leaflets that open up when blood flows forward and close very tightly when the heart stops pumping. So, blood flows forward, but it can't flow backwards. This is the appearance of a valve that we excised from a patient with carcinoid heart disease and put in a new valve. You can see that the leaflets have become thickened because of scar tissue and when we replace this thickened scarred valve with a new valve. There are several of you in the audience who are my patients that I know have undergone this surgery and others are going to be undergoing the surgery. and it can produce a remarkable change in the quality of life. We are doing this now because we have better methods of controlling the metastatic disease.

This is a cartoon showing the appearance of the heart muscle. This is the right ventricle - the pumping chamber, this is the left ventricle. This scar tissue which we call endomyocardial fibrosis usually affects the tricuspid valve which separates that right atrium from the right ventricle and the pulmonary valve which separates the right ventricle from the pulmonary artery. It is uncommon for the fibrosis to affect the valves on the left side of the heart because this serotonin-rich blood goes out to the lungs and there are enzymes in the lungs just like there are in the liver that break down the serotonin. So when the blood returns to the left side of the heart the serotonin levels are much lower.

How many of you have heard of the heart disease associated with diet Fen-Phen? (Show of hands) Most of you. Fen-Phen was the combination of two drugs; fenfluramine and phentermine. It turns out that that combination of drugs causes heart disease that is identical to the heart disease seen with carcinoid tumors and it is identical to the heart disease seen with drug that was used for migraine headaches called Sansert and a drug called ergotamine which is still used for migraine headaches and I don't have the molecule of the phentermine up here, but it has a similar basic structure to serotonin, methysergide, and ergotamine and all four of these compounds can cause thickening of the heart valves. This slide is shown because I wanted to emphasize that we are woefully in need of better chemotherapeutic drugs. The best that has been achieved so far is with streptozocin plus 5-FU, about a 30% response rate, but the therapy did not impact on survival in a meaningful way. We have done many trials over the years looking at new chemotherapy agents and the low response rates seen thus far demand further clinical trials.

One approach to treatment that has been quite successful is hepatic artery embolization. During that procedure a catheter is placed in the groin and then threaded up to the hepatic artery that supplies the tumors in the liver. We inject a material called embospheres into the artery and it occludes the blood flow to the tumors and in more than 80% of patients the tumors will show significant tumor shrinkage. By following that with chemotherapy using doxorubicin plus dacarbazine (DTIC) alternating every other month with 5FU plus streptozocin, we found that we could prolong the duration of response by threefold. We don't always use chemotherapy after embolization and the reason is that we are relying increasingly on the growth inhibiting properties of Sandostatin to bring about prolongation of response, but sometimes when the tumors get big and bulky and we get some shrinkage we'll try to maximize the benefit of embolization and give chemotherapy afterwards. So, it is a situation that is individualized for each patient at the present time. That is the rationale for doing embolization and then in some instances following it with chemotherapy.

Now, I know that there are some people in the audience, a handful, who have islet cell carcinoma and that is a kissing cousin to carcinoid tumors. But unlike carcinoid tumors which usually arise in the airway and the intestine, these islet cell tumors arise in the pancreas and they are substantially more responsive to chemotherapy. A randomized study is a study in which the patient does not decide, the doctor does not decide, but you are assigned to one of these three treatments by computer randomization and that is done when we have treatment that we know works. We have a new drug that looks like it could be safer and have fewer side effects and an experimental drug that we need to evaluate against the standard drug. So, in this randomized study which involved about

120 patients at multiple cancer centers around the U.S. we found after follow-up that 69% of patients getting the combination of streptozocin plus doxorubicin, had objective tumor regression compared with only 45% who got what at that time had been considered the gold standard (5FU plus Streptozocin). The point here is that islet cell carcinomas are much more responsive to chemotherapy than carcinoid tumors and we hope that by continuing to do clinical trials that we can find chemotherapy drugs or combination treatments that are much more effective for carcinoid tumors.

Now, we are careful to review the tissue on every patient that we see in consultation and we want to do that because we want to determine if the tumor is a so called well differentiated tumor or a poorly differentiated tumor, also called anaplastic. The anaplastic carcinoid tumors are the tumors that when we look under the microscope have lots of cells that are dividing. These are tumors that are faster growing. Well-differentiated carcinoid tumors were called by one of my pathology colleagues at Mayo years ago “cancer in slow motion” because they may sit there for a long time and change very, very little. So one of the critical things when we first see a new patient is to determine if the carcinoid is well differentiated or poorly differentiated.

In this series, when we looked at the combination of two different drugs; VP16 and platinum we saw that 12 out of the 18 patients with this poorly differentiated tumor had tumor shrinkage so it was very active in that group of patients, but it was ineffective causing tumor shrinkage in only 7% of the well differentiated tumors. We never use this combination for the garden variety, well-differentiated slow growing carcinoid tumors, but for the more poorly differentiated, aggressive carcinoid tumors, it is highly effective.

Most of these well-differentiated tumors are somatostatin receptor positive meaning they have receptors on the surface of the cell. Most of the poorly differentiated tumors are somatostatin receptor negative. When we do an Octreoscan which tells us whether the tumor has receptors or not and we don’t see the tumors that may mean that the tumor has become more aggressive. I will repeat a biopsy to see if it’s this poorly differentiated anaplastic type. Because if it is, it opens a new therapeutic opportunity, namely VP16 and platinum systemic chemotherapy.

The next area I’d like to cover is somatostatin and I know that Dr. O’Dorisio will have more to say about this. Somatostatin is ubiquitously distributed in the human body. We have it in out pituitary, our thyroid, our stomach, our pancreas, and our intestine. It was first discovered by Roger Guilleman who is one of my professors at Baylor and Andrew Schalley who shared the Nobel Prize for it. It is made up of fourteen different amino acids and amino acids shown in yellow here are the amino acids that are important in binding to the receptor on carcinoid tumor cell surfaces. Sandoz synthesized hundreds of synthetic somatostatin molecules and the first one that we had available for use in humans at that time was code named SMS 201-995. That is the drug that is now available as octreotide or the commercial name is Sandostatin. It is a shortened version of naturally occurring somatostatin. This drug could be given by subcutaneous injection and this compound after injection has a half-life of two hours as opposed to naturally occurring somatostatin, which has a half-life of only two minutes. Thus, it became practical to use in humans who could give themselves three shots per day.

In our first series of 66 patients treated with Sandostatin for the malignant carcinoid syndrome, we observed that 87% of the patients had relief of flushing, and in nearly 60%, the improvement was complete. The flushing was totally controlled. Diarrhea was improved in three-quarters of the patients. By improved, I mean the frequency of bowel movements and stool volume decreased by 50%. In one-third patients developed normal formed bowel movements. The biochemical marker 5HIAA in the urine decreased by 50% or more in three-quarters of the patients. So, not only did it bring about improvement in symptoms of flushing and diarrhea, but it lowered the level of serotonin by more than half in three-quarters of the patients.

One of the interesting things that we observed back in 1986 or 1987 was that patients who went on Sandostatin had all had progressive disease before they went on Sandostatin and suddenly many of the tumors became stable and remained stable for months or in some cases years. When we analyzed the survival of patients on chronic Sandostatin and compared it to the survival of patients getting chemotherapy where only half of the patients were still alive at one year, we saw that more

than half of our patients were still alive at three years. This was the initial evidence that Sandostatin, although it causes tumor shrinkage uncommonly, does result in prolongation of life because of the growth inhibitory effect on the tumor cells. Dr. Reubi, my colleague in Switzerland, and I were interested in finding out how come many, most, but not all patients with carcinoid tumors responded to Sandostatin therapy. He was able to hook a radioactive molecule onto a somatostatin compound that had a different amino acid here in position three called tyrosine and this radioactive iodine could be used in the laboratory and what he did is something called in vitro (that is in the lab, not in the body) autoradiography. We got biopsy specimens either with ultrasound guidance in the radiology department or from patients who were going to surgery to have partial liver resections or bowel resection. I sent them on dry ice to Dr. Reubi and he incubated the tissue with this iodine labeled somatostatin. In the laboratory then after it had incubated, it was exposed to photo-emulsion material and if the tumor had receptors for somatostatin it bound tightly and the radioactive iodine gave off energy that turned that photo-emulsion black. So, here is a standard pathology stain showing a core of tumor. This is about the size of a #2 pencil led and it is about half an inch long and when Dr. Reubi did the analysis with this iodine labeled compound he saw that all of these tumor cells expressed somatostatin receptors and that is why this is black. This just shows nonspecific staining. He analyzed all this tissue and provided me with the results before he knew what had happened when we gave the patient Sandostatin therapy. This patient who had dense homogeneously distributed somatostatin receptors was producing the hormone vasoactive intestinal peptide, and the patient was having about eight quarts of diarrhea per day. After starting Sandostatin, the VIP level went from 600 down to less than 50 which is normal. That correlated with the presence of receptors. This patient whose tumor was not expressing somatostatin receptors was producing ACTH and when we treated her with Sandostatin, the ACTH level progressively rose. So if no receptors for somatostatin are present, then you do not respond to Sandostatin.

When we analyzed these 31 patients that Dr. Reubi had studied, 9 of them who have strongly positive receptors all had a major hormonal response when they got Sandostatin therapy and a major response we defined as a 50% decrease in the biochemical marker hormone. The 7 patients who had no somatostatin receptors on their tumors cells, 6 of the 7 had no response whatsoever to Sandostatin therapy. So, this was the initial observation that the somatostatin receptors on the carcinoid tumor cells and islet cell tumors mediated the response to Sandostatin therapy.

The next part of this evolving story came about when Professor Krenning and his colleagues at Rotterdam were able to make a different radioactive compound with indium-111, linked by way of a chelator which is just a connecting compound, to the somatostatin that we had been using clinically. Indium-111 is a radioisotope that gives a form of radiation called gamma rays. Many of you have been injected with this compound which is known commercially as Octreoscan. You can see that the linker and the radioactive compound here don’t interfere with these crucial amino acids that bind to the Somatostatin receptor. I am going to show a couple of examples of Octreoscan. Here is a CT scan showing multiple tumors scattered throughout the liver and this is fusion imaging where we take the digital information from the Octreoscan and fuse it by way of a software program with the digital information from the CT scan. You can see that this area of tumor in the liver seen on the CT scan is hot on the Octreoscan meaning that this has somatostatin receptors. The kidneys show up hot because that’s where the material that does not bind to the tumor cells is excreted. This is a patient who was having intermittent bloating, distention and abdominal pain and we had done small bowel x-rays and had not been able to find a small bowel tumor. But, when she had the Octreoscan with fusion imaging, this area lit up quite intensely and that was the site of the primary tumor. We were able to offer her surgery and resect this area and she had complete relief of the obstructive symptoms. This is a patient with extensive carcinoid in the liver and fusion imaging shows that all of these tumors express somatostatin receptors. This patient’s carcinoid tumor started in the stomach and here we can see the uptake in the carcinoid tumors in the stomach.

Now, I’d like to just mention briefly some studies that were done initially by Professor Krenning using the diagnostic drug Octreoscan as a therapy. He did this because when the radioisotope decays it gives off something called Auger electrons. Auger electrons dissipate all their energy within just a few microns and a cell is approximately 10 microns in diameter. So these Auger electrons dissipate all their energy within a cell. What happens when somatostatin or Sandostatin binds to the receptor on the tumor cells surface, it gets taken inside the cell, the receptor gets recycled and the radioactive material and linker and one of the amino acids ends up inside the cell in what are called

lysosomes. The energy given off by this indium is close enough to the nucleus that it can damage DNA. Professor Krenning and his colleagues first did a series of experiments in animals. They injected a million tumor cells which had somatostatin receptors into the portal vein which supplies the liver and these rats were then treated either with the Octreoscan or in the control group of rats they got the Octreotide and the chelator, but it did not have a radioisotope attached to it. These are fast growing experimental tumors and the animals had to be sacrificed by three weeks because the tumor if left untreated virtually replaces the liver in these rats.

Here is what happened in the six livers of the rats that got just plain octreotide without the radioisotope attached to it. You can see that all six of the livers had extensive replacement by tumor, which is shown by this appearance. The normal liver looks more like that. All six of these rats that just got cold non-radioactive octreotide had extensive tumors. The six animals that got the radioisotope attached to the octreotide were not cured, but you can see a striking decrease in the number of tumors in these animals that were sacrificed at 21 days. This was very convincing evidence that the indium-111 might have therapeutic potential in humans. In a series of patients treated in the Netherlands with up to eight or ten injections of Octreoscan at 30 times the usual diagnostic dose, there was significant reduction in the size of the tumors in some of the patients. This is an Octreoscan from a patient with another type of neuroendocrine tumor called paraganglionoma. All these are areas of tumor in the neck and above the collarbone here. This tumor had been progressing back in 1993. There is the tumor and by July the following summer it had enlarged to that size. At this point, the patient was started on the Octreoscan therapeutically and after three treatments you can see that the tumor had gotten smaller and after eight treatments a year later you can see the tumor was substantially smaller compared to before treatment. What Dr. Krenning observed in the 21 patients who got eight or more doses and were all progressing before treatment was that a total of 6 of the patients had tumor shrinkage. This is an incredibly expensive form of therapy and each injection, if the patient had been charged, would have cost 20,000 to 25,000 dollars. What came along next was the yttrium-90 labeled compound. We observed in this earlier trial of Dr. Krenning's that very faint uptake usually was not associated with the response of therapy. The patients who had grade 4 or very intense uptake, were the ones who were most likely to benefit. So, when we launched the trials with yttrium-90 which I am going to move to next we tried to select patients who had grade 3 or grade 4 uptake on the Octreoscan.

In the remaining time, I would like to share with you some of the results from the initial human trials using the yttrium-90 labeled somatostatin. These were the so-called Phase I studies. Some of you in the audience were involved in these Phase I studies. Others have been involved in the Phase II studies. The Phase I studies were done at three centers; Brussels, Rotterdam and Tampa.

The Phase II studies were done at a number of centers around the world including five centers in Australia, multiple centers in the U.S. including Dr. O'Dorisio's center, here at Moffitt and several centers in Europe. As many of you know, the Phase II studies have now met their targeted accrual goal and they have been closed by Novartis. Many patients are still being treated. We had a preliminary meeting with the FDA just three weeks ago to try and keep this drug on track and hopefully it will be approved in late 2003 or early 2004. We don't have results from the Phase II study because many of the patients are still undergoing therapy and its from so many different centers that there has not been a pooling of the data and analysis yet. I'll share with you what we have learned from Phase I study.

This therapy is based upon the molecule that we have been talking about all day. This is the Sandostatin (octreotide) and then there is a different linker here than I showed you for the Octreoscan. This is a linker called DOTA and DOTA is attached to a Sandostatin molecule and it functions like a cage for yttrium. It binds the yttrium incredibly tightly in the cage and it can't get out. Yttrium emits a form of radiation energy called beta rays. If yttrium is not bound to this molecule tightly, it goes to the bone and can cause bone marrow toxicity. So this chelator works like superglue and we don't see free yttrium circulating in the body. We did biodistribution studies in humans to determine how the body handles the drug. Some of you in the audience have been to Brussels, Belgium to participate in these early studies. When we started the Phase I trial, the FDA demanded that we determine how this molecule was handled in the human body. We did these studies in Brussels, Belgium because there was a research cyclotron there that could produce a molecule called yttrium-86. With yttrium-86 we could see how the body handled the compound

because it emits something called a positron and we can use a PET scan to trace it. I am going to go over some of these slides rather briefly so I can get to the meat of the matter. The yttrium-86 linked to this compound allowed us to trace the pattern of excretion in the human body. Here we see the normal liver, we see the kidneys, we see the spleen and this is the bladder. This is a patient with carcinoid tumor in the liver who got the yttrium-86 study in Brussels and you can see the uptake in the liver tumors here. We knew that the drug, which did not bind to the tumors, was excreted in the urine so we were concerned about toxicity from the radiation to the kidneys. In experimental monkeys given progressively higher doses of the drug to see what toxicity occurred, we saw that the very, very high doses - fifty times higher that whatever we use in human trials - the monkeys died because of kidney failure.

So, in an effort to try and protect the kidneys when we started these trials in humans we used an infusion of amino acids to try and minimize the amount of radiation to the kidneys. We used the amino acids to reduce renal uptake because when the drug which doesn't bind to the tumor cells is filtered by the glomeruli in the kidneys the kidneys try to hang on to it by reabsorbing it. We basically flooded the kidneys with amino acids and they acted by competitively inhibiting the uptake of the radiolabeled peptide at the level of the kidney tubules. What we learned was that we can decrease the amount of renal radiation exposure by giving 2 liters of amino acids by as much as 40%. This is a visual example of that. What we have here on the top three panels is the appearance of the PET study with yttrium-86 at 4 hours, 24 hours, and 48 hours. The patients were their own controls so on one occasion they got the yttrium-86 without amino acids and then a week later they got two liters of this amino acid solution over four hours and even visually you can see that the amount of uptake in the kidney is substantially reduced when we gave amino acids. This was true at 4 hours, at 24 hours, as well as at 48 hours. Happily the amino acids did not interfere with the uptake of the drug in the tumors.

So, in the first 6 patients that we studied in Brussels we observed this favorable reduction in kidney radiation exposure by amino acid infusion and subsequently all patients who got the treatment received amino acid infusion based on this promising result.

The magnitude of reduction in renal radiation exposure varied from about 25 up to 40%. This shows that although it reduced renal radiation exposure it did not change the amount of radiation that the tumors received at any one of the time points. Infusing amino acids for ten hours was a little better than 4 hours, but not so much that it has become routine practice.

We concluded from those studies in Brussels that mixed amino acids reduce renal exposure during this peptide based radiotherapy but it was associated with some nausea and vomiting. We can control that somewhat by antinausea drugs and the rate of infusion of the amino acids.

We did a number of other studies during Phase I that I don't have time go to into today and I'd like to conclude by sharing with you our experience in the formal Phase I trial. All patients had undergone these biodistribution studies in Brussels before entering the Phase I trial either in Rotterdam or Albuquerque where I was before coming to Moffitt and then over the last three years here at the Moffitt Cancer Center. This trial is still ongoing as we still have some questions we are trying to answer about how to optimize the protection of the kidneys. A Phase I study is basically a study to look for safety. Phase I studies are not efficacy studies. They are basically the first use of a novel agent in humans. Of course, we always hope that promising results we have seen in the laboratory or in experimental animals will translate into positive results in humans, but when we do Phase I studies we start with very low doses because we don't want to do any harm. We follow the first 3 patients for six weeks and then go to the next higher dose and keep escalating the dose progressively higher and higher if no toxicity is seen. We were treating primarily patients with carcinoid or islet cell tumors so it wasn't like we were treating some patients with melanoma and some with kidney cancer and some with Hodgkin's disease. We were treating a homogeneous group of patients and we hope that we could make observations about the potential anti-tumor effect as well as safety.

Peptide receptor radiotherapy (PRRT) is the broad term that we use for this field because octreotide (Sandostatin) is a peptide. We are targeting receptors with a radionuclide given therapeutically. So, PRRT is one acronym that we have been using. In the medical literature this is the name you will

see. Novartis code-named their compound SMT487. For those of you who are Internet mavens, you may have come across what is called yttrium-90 dotatoc. That is an abbreviation for dota-the chelator, plus tyrosine Octreotide. If this drug is approved by the FDA it will be called OctreoTher. Novartis called this study B151. BRTN in these slides stands for Brussels, Rotterdam, Tampa, and Novartis.

We treated a total of 42 patients in this study and most of them had carcinoid or islet cell tumors, 11 had neuro-endocrine tumors where we could not find the primary tumor. Thirty-four of the 42 patients had progressive disease when they started on therapy. Eight of them had had no documented progression in the preceding year so they were called stable. Remember this was a Phase I dose escalating study, so the first dose in these 42 patients ranged from 36 millicuries up to 291 millicuries. The cumulative dose after four cycles of therapy ranged from 47 millicuries up to over 700 millicuries. We are always looking for evidence of safety and what is called dose-limiting toxicity particularly in the Phase I study. If three patients are treated at a given level and one of them experiences a dose limiting toxicity, then before escalating to the next dose we treat three more patients at that same dose level and if those three patients do not experience any toxicity then we keep escalating. So, two patients out of six have to experience a dose limiting toxicity before we will conclude it is not safe to go any higher. We did see three dose limiting toxicities. One patient had abnormal liver function tests, one low platelet count, and one myelodysplastic syndrome, but when three additional patients were treated at that same dose level we did not see toxicity so that is why the study has continued.

The toxicity that we have seen so far I have just mentioned. There has been about a 16-18% decrease in kidney function now with three year follow-up, but this drug is remarkably safe using the amino acids for kidney protection. We have seen some mild decreases in the blood counts, but importantly since somatostatin receptors are present in so many other tissues in the body we looked to see if there was any disturbance of the normal pituitary thyroid function, pituitary-adrenal function, or pituitary ovarian function. We did not see any. The islet cells in the pancreas are rich in somatostatin receptors and the islet cells produce insulin normally, but none of our patients have developed diabetes mellitus.

I would like to show just a few patient examples before concluding. This is a patient with a neuroendocrine tumor producing gastrin and the tumors on the Octreoscan are shown here as the dark black spots. This was one of the tumors that we measured as 10 x 10 millimeters at the baseline. This is that served as the “indicator lesion”. We measure the tumor (lesion) to see if it was getting any smaller. You can see that after four cycles of therapy there is decrease in the uptake on the Octreoscan and a reduction in the size of the tumor. High levels of gastrin in this patient were associated with very high levels of stomach acid production and the patient had horrific diarrhea, which completely resolved. With time, her gastrin eventually normalized as did the chromogranin. It took over a year for the chromogranin to normalize and actually it initially increased perhaps as a result of tumor cell death liberating chromogranin. In the 32 out of 42 patients who received the planned dose of therapy, half of the patients, 16 of 32, had symptomatic improvement. By this I mean improvement in their performance status, their quality of life and reduction in their symptoms whether it be flushing, diarrhea, pain, loss of appetite and so forth. Two of the patients whose tumors were producing excess insulin were requiring continuous infusion of glucose to keep them from being hypoglycemic had normalization of their blood sugar levels and were able to stop receiving glucose by infusion.

Oncologists like to speak about partial remissions, complete remissions, minor responses. With a partial remission the tumor has decreased by more than 50% in size. A minor response means that the tumor has decreased between 25 and 49% in size. We saw that in 24% of cases. Seventeen of the patients developed stability of disease after having progression, that is about half of patients, and nine of the patients continued to have progressive disease in spite of therapy. This breaks down the results according to the patients who were clearly progressive before they went on therapy and those that were stable when they went on therapy and you can see that of the patients who were clearly progressive before they went on therapy about half of them became stable and we saw about a third of them progress in spite of treatment and then the remainder have tumor shrinkage (objective tumor response). In the eight patients who were stable when they went on this Phase I study, six of the eight remained stable with a follow-up of over two and a half years. When we

analyze these results in comparison with some trials that had been done in Milan and in Basel, Switzerland the overall number of patients treated is 142. They were not using Novartis compound in Milan or Basel, but it was a compound that as far as we know was identical and the overall results were 20% objective tumor shrinkage, about 64% of patients who were progressive developed stable disease or minor response. So, their data really corroborated what we had observed in the Phase I study.

How does this compare with Sandostatin, the non-radioactive somatostatin compound which many of you are receiving? Professor Arnold did a literature review and found 167 published cases treated with the long-acting somatostatin analogs and 2% of the patients in this series had objective tumor shrinkage. We talked about the fact that although tumor shrinkage is uncommon, stability of disease is common. The trial that Dr. Krenning and later Dr. Anthony at LSU and Professor Modlin at Yale did using the Octreoscan or indium-111 therapeutically, got an 8% objective tumor response rate. In our trial as well as the other two trials in Europe the overall response rate was 20% tumor shrinkage and nearly 60% conversion from progressive to stable disease. We are eager to look at ways to substantially improve this treatment and one of the things that is currently being evaluated in Rotterdam is another radionuclide called lutetium-177. We are also looking at other types of somatostatin analogs that have even greater affinity for the somatostatin receptor.

One of the new ones called octreotate binds with four times the affinity to the somatostatin receptor so it should deliver a higher dose of cell-killing radiation therapy. I am personally interested in combining these treatments with chemotherapy drugs that enhance the effects of radiation. The combination of chemotherapy with peptide receptor radiotherapy could hopefully enhance the therapeutic benefit.

I focused primarily on peptide receptor radiotherapy because I think it is one of the most exciting new developments in the field of carcinoid treatment, but we are not abandoning our search for other ways of targeting the molecular mechanisms that are behind tumor progression. One of the very important things that allows tumors to continue to grow is the formation of new blood vessels. The process I is called angiogenesis. There are a number of compounds that are anti-angiogenic in nature. It is interesting there is a lot of excitement in the medical literature and in the lay press now about anti-angiogenesis compounds, but it turns out that Sandostatin, in fact, is one of the most effective compounds in terms of anti-angiogenesis. It inhibits new blood vessel formation and Professor Woltering who is at LSU has done some elegant experiments documenting that. So, we have been doing anti-angiogenesis therapy for twenty years, Tom, and it just got on the front page of the Wall Street Journal a couple of years ago when the endostatin trials in mice were published.

There is an ongoing trial in the United States now evaluating endostatin in islet cell cancer patients. We hope to have access to this compound for carcinoid patients if those trials in islet cell patients look encouraging and safe. We are also going to be evaluating a new drug called Epothilone-B and that is going before our scientific review committee on Monday. It should be available in two or three months. It is going to be a multi-center trial I think involving five centers around the U.S. By doing these multi-center trials in which physicians around the country that focus primarily on carcinoid tumors in their practice, we can answer questions much more quickly. We can answer questions sometimes in two or three months that might take a single center more than a year so those trials will hopefully be starting in two or three months. There are other exciting products in the pipeline. There is a new analog of somatostatin with a broader range of binding to the various types of somatostatin receptors. I encourage those of you who need treatment to participate in clinical trials."

* Footnote: Regarding alcohol in cooking: Source: The Oxford Companion To FOOD.
by Alan Davidson. Publ; Oxford University Press, Inc. NY 1999; page 10

" It is sometimes debated whether any alcohol will remain in a stew after cooking. The answer is 'almost certainly not'. The theory of stews demands that they should be cooked at tmperatures high enough to coagulate the proteins in the meat (over 60C), but not as high as high as the boiling point of water (100 C) . The practice of most cooks is to let a stew perceptibly 'simmer', at a temperature somewhere around 95 C (203 F) . Ethyl alcohol vaporizes at 78 C (172 F), so any alcohol in the cooking liquid of conventially prepared stew will be evaporated ('boiled off'). An

alcoholoc drink used to FLAME food will inevitably lose its alcohol in the heat of the process."

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