

Diagnosing and Treating Carcinoid: The Dana-Farber Experience

Presented by

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Introduction Lecture - Richard R.P. Warner M.D.

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Welcome. I am happy to see everybody here and hope and expect that this will be an informative and useful session. This is, as you know, the fourth of these regional meetings in which all of the chapters of metropolitan New York Carcinoid Support Group convene, or at least representatives of each area are present, and we hope that you'll each pass on whatever you learn here to your fellow members in your own chapters.

I have just a few words to say by way of introduction -- Carcinoid is the term applied to the tumor that we're so interested in, which is the major tumor of the neuroendocrine tumor family. So much of what I have to say and Dr. Kulke, our guest speaker, will have to say, applies to some of the other less common tumors, also neuroendocrine tumors. The term "carcinoid" really originated about a century ago, applied by a German pathologist to this group of tumors which he studied and which arose in the intestine and looked different from ordinary carcinomas, but yet weren't quite entirely benign. Therefore, he coined the term "carcinoid" as meaning an in-between type of growth of intermediate type of malignancy, yet looking like carcinoma. Just like we know the term, humanoid, in science fiction as applied to a robotic biological creation that's like a human but really not quite the same, so carcinoid is an in-between type of growth.

Originally this was an extremely rare tumor, but in the last fifteen years it has been diagnosed with greater frequency, though still quite uncommon. Presently, there are about 3,000 to perhaps 4,000 new cases appearing and reported in the United States every year. That means that there are about 50,000 with carcinoid of clinically significant degree walking around and a smaller number of people with other neuroendocrine tumors. Of course this is rather uncommon when viewed from the perspective of the more frequently encountered growths like cancer of the colon, breast, prostate, etc. Furthermore, although originally it was thought that all carcinoids were really very low-level malignancies, there is a small percentage of cases, perhaps 20%, in which the tumors do behave more malignantly and are more aggressive than the majority. Therefore the degree of malignancy of these tumors ranges over a full spectrum and this raises some confusion in minds of average medical practitioners since they see so few of any of these cases and there are all levels of aggressiveness available in treatment that might be applied as well as a considerable variety of possible treatments. Thus, it is almost bewildering to one who doesn't really work a great deal in this field. Furthermore, having had an experience with perhaps only one or two cases, it is impossible to apply that experience to the next case because they may differ so much. Because of this, there is a wide variation in the philosophy toward treating patients with carcinoid. It may vary from a very conservative "wait-and-see" attitude, which I'm sure you've all heard about, and which may be appropriate in some circumstances, to a very aggressive proactive practice in dealing with patients, which is perhaps more appropriate for more aggressive tumors, and maybe even appropriate for many of the indolent and slow-growing ones. The proactive aggressive

approach is beginning to gain more favor and more adherence in some medical centers where more of these cases are treated. Evidence to support the appropriateness of this different approach to treating is slowly evolving.

Now to preface what our guest will have to say, I want to summarize so it will be clear to everybody regarding treatment in general for carcinoid and especially carcinoid syndrome. There are three general categories of treatment and items from each category may be applied simultaneously or in sequence depending on the needs in a given case. First supportive measures, next surgical measures and, finally, anti-proliferative measures. The latter means chemotherapy and other modalities of treatment that will inhibit tumor cells from growing or kill them.

In review of the medical supportive treatment, we have antidiarrheal treatments that include everything from drugs with which you are familiar, such as Lomotil and Imodium, Tincture of Opium, Cyproheptadine (Periactin), and other drugs that work in other ways. These also have as their main goal prevention of diarrhea. These include Cholestyramine, pancreatic extracts and, finally and most important, Octreotide. In the United States and much of the world, that is the most important drug used for this purpose in carcinoid syndrome and is known as Sandostatin.

Also supportive are nutritional factors and I know you are aware that they play an important role in carcinoid syndrome, perhaps more so than in many other diseases. This includes the replacement of electrolytes and fluid lost in the course of diarrhea, anti-ulcer medicines because of the frequency with which ulcers develop in carcinoid syndrome, as well as a variety of other medications and dietary measures to prevent fibrosis development in the heart and in other parts of the body.

The next category of treatment is surgery. There are a number of different surgical procedures that might be used and applied in these tumors. First, of course, is the biopsy for diagnosis. In fact, this is almost necessary always and is critical because it is usually unreasonable and improper to resign a patient to prolonged and perhaps aggressive treatment without absolute proof of the diagnosis. After that, there is resection of a tumor and of metastases in an effort to cure or even just de-bulk. Since these tumors most often grow slowly, reducing the volume of tumor may provide extra years of useful, comfortable life. There are other means of destroying tumors that also may be employed and these include radio frequency ablation, freezing the tumors with cryoablation, interfering with their circulation in the liver by embolus or chemoembolus injection. We can replace diseased heart valves, which often is a great help. We can relieve the collection of fluid in the abdomen by drainage in one way or another. In certain situations, such as obstructive jaundice because of bile duct compression or obstruction by tumors, we can insert a stent. We can also put stents in big blood vessels that are being obstructed and, finally, but not very often, we can do a liver transplant. This is not enjoying a great deal of application nowadays because it has not been proven to be better than conventional treatment except in some very selected situations.

The third category of treatment is antiproliferative treatment. It is important to recognize that biotherapy is not the same as chemotherapy. In this form of treatment, we give drugs that alter the body's metabolism, or the way cells grow, so that the body's own immunological status can improve and enable it to better combat the tumors. At the present time, this involves Somatostatin derivatives such as Sandostatin. To this is often added Alpha-Interferon. These drugs also act as inhibitors of new blood vessel formation and I'm sure you will hear more about this. Radiotherapy is also a treatment technique used, either as delivered by external beam to irradiate a painful bone lesion, or internally by the injection of radioisotopes either systemically or into a specific region such as blood vessels that supply tumors in the liver. Currently this treatment employs mostly Yttrium90. Indium111 was formerly used with rather limited success. In some quarters, MIBG labeled with a radioactive Iodine isotope has been used, but it has been of limited benefit. Now emerging is Lutetium177 attached to a Somatostatin derivative. This is still experimental, but has been highly regarded in initial reports. Finally, chemotherapy is sometimes used. This involves the administration of one or several of a wide variety of toxic agents that have varying degrees of effectiveness in regressing or deteriorating tumor cells.

Our guest lecturer today, Dr. Mathew Kulke, comes from Dana Farber Cancer Institute. He is highly regarded as an experienced leader in clinical trials in chemotherapy and he is going to tell us how they treat Carcinoid and other neuroendocrine tumors at his institution. In particular, we hope, he

will tell us what clinical trials are going on, not only at his institution, but what he knows of elsewhere in the country and what the results are of some of these trials that have been completed and maybe some that are still in progress and are beginning to show some response. At the completion of his talk, we will have a short break and then there will be an opportunity to ask questions.

Dr. Matthew Kulke

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Thank you very much. I have to say that over the past several years, I kept on hearing from all my patients what a wonderful and supportive group you all have down here in New York and it truly is an honor and a privilege to finally be able to come down and meet you and also speak to you. What I would like to do in the next hour or so is initially to give a general overview of neuroendocrine tumors, including both pancreatic endocrine tumors and carcinoid tumors. And then in the second half of the talk, we'll talk more specifically about some of the treatments and especially some of the clinical trials that are going on both at Dana Farber and at other sites around the country.

There actually remains quite a bit of confusion not just among patients but also among physicians, about what exactly neuroendocrine tumors are. We generally subdivide neuroendocrine tumors into two large groups. The first general group are pancreatic endocrine tumors, also sometimes called islet cell tumors. And the second group, of course, are carcinoid tumors. These two tumor types are in many ways very similar. They have a similar histological appearance when you look at them under the microscope - for example, they both contain granules that contain hormones that can be secreted into the bloodstream and can cause a variety of different syndromes. The clinical course of patients with pancreatic endocrine tumors and carcinoid tumors can also be similar. They are often characterized by a slow, indolent clinical course with many people feeling perfectly well for many years. Where they do differ in some respects are in the specific hormonal syndromes.

One of the first patients described with a neuroendocrine tumor was thought to resemble an alcoholic. It turned out that his very perceptive personal physician found out that he was really experiencing symptoms of low blood sugar or hypoglycemia. These symptoms include confusion, blurred vision, and even seizures in severe cases. In addition, they include autonomic dysfunction-- symptoms like sweating, weakness and nausea. This patient had a pancreatic endocrine tumor called an insulinoma that secretes large amounts of insulin and causes episodic episodes of low blood sugar. The patient went on to have surgery, and did very well.

There is another hormone that's really in some ways the opposite of insulin, and causes high blood sugar. This hormone is also secreted in the pancreas and is called glucagons. As one might expect, patients who have glucagonomas fairly frequently have symptoms of diabetes. Another syndrome that is specifically associated with glucagonoma is called necrolytic migratory erythema. This is a red rash that typically involves the pelvic area, and can sometimes extend to the trunk.

Yet another type of pancreatic endocrine tumor is called VIPoma. This kind of tumor secretes another hormone called VIP, which is short for vasoactive intestinal peptide. There's a syndrome that goes along with this called Verner-Morrison syndrome. Patients who have this sort of syndrome have very profound watery diarrhea. This is because VIP has many effects on the intestine, including inhibited absorption of electrolytes, like chloride, bicarbonate and potassium.

A fourth kind of pancreatic endocrine is a gastrinoma. This tumor secretes gastrin, yet another hormone, resulting in a syndrome called the Zollinger Ellison Syndrome. Gastrin causes high acid secretion in the stomach. People who have gastrinomas very often have abdominal pain due to peptic ulcer disease, or reflux esophagitis. They can also have diarrhea and pain with swallowing, or dysphasia, which is simply difficulty swallowing.

Initially, when faced with a patient who has one of these hormonal syndromes from a pancreatic endocrine tumor, the first challenge is how to make them feel better. How to stabilize them. There are different ways of doing this. A patient with an insulinoma, for example, sometimes will do quite

well just with frequent administration of carbohydrates, raising their blood sugar so that they don't have the very sudden and profound episodes of low blood sugar. Patients with glucagonoma interestingly can do quite well with injections of octreotide. Similarly, patients with VIPoma, the syndrome that results in profound watery diarrhea can also respond extremely well initially to octreotide. And, finally, patients with gastrinoma can do well with anti-acid therapies like proton pump inhibitors, many of which are available.

Surgical resection still remains the only way to cure this sort of tumor. There is a genetic syndrome called MEN-1, or multiple endocrine neoplasia type 1 that some people may have heard about. This is a syndrome where multiple endocrine tumors can be found and can occur. So it's important to keep that in mind and not miss one of these other tumors in such patients. And, in general, when one can complete resect pancreatic endocrine tumors, the prognosis is excellent.

Carcinoid tumors are somewhat more common than pancreatic endocrine tumors. The overall incidence of clinically relevant tumors is around one or two per hundred thousand population per year. One interesting fact is that the incidence in autopsy series is four times higher, eight per hundred thousand population per year. What this indicates is that carcinoid tumors very often have a slow and indolent clinical course. In fact, probably more people die with carcinoid tumors than of carcinoid tumors. This is an important distinction that really makes carcinoid tumors and other endocrine tumors very different from the other types of cancer we typically hear about.

The way we classify carcinoid tumors is by a theoretical division of the embryonic gut. Foregut carcinoid tumors typically include carcinoid tumors that start in the lungs and bronchi, sometimes also in the stomach. Midgut carcinoid tumors are tumors that start in the small intestine, the appendix or the proximal large intestine. And hindgut carcinoid tumors typically are rectal carcinoid tumors. The clinical presentations, and certainly the local management of some of these tumors differs quite a bit.

Bronchial carcinoid tumors comprise about two percent of all primary lung tumors. These are often central in location, located closer to the heart rather than peripherally out in the lungs. Patients with bronchial carcinoid tumors frequently will have symptoms of cough, not uncommonly having been diagnosed with symptoms of asthma, sometimes for ten to fifteen years before the actual tumor was noted. Bronchial carcinoid tumors can cause some neuroendocrine symptoms. Interestingly, the classic carcinoid syndrome, with flushing and diarrhea, is almost unheard of in patients with bronchial carcinoid tumors. More frequently patients will have Cushing's Syndrome, which results in high levels of cortisol, weight gain and facial puffiness.

Particularly with bronchial carcinoid tumors, it's important to think about various different subcategories. Bronchial carcinoid tumors can often be categorized as either typical or atypical. Typical carcinoid tumors generally have a very uniform pattern of blue cells. If one were to look at this close-up with a high powered microscope, one would be very hard-pressed to see areas of mitosis, or areas of cell division. This indicates that typical bronchial carcinoid tumors generally grow very slowly, and don't metastasize all that commonly. In contrast, with atypical bronchial carcinoid tumors, one can see areas of necrosis, or cell death. If one were to look at this at high power, one would see frequent mitosis, frequent areas of cell division. So this is a more aggressive form of carcinoid tumor. This makes a big difference in terms of prognosis. When these tumors are cut out, typical bronchial carcinoid tumors, have very high cure rates. In contrast, the atypical bronchial carcinoid tumors have a more aggressive course.

For typical carcinoid tumors, a conservative resection or smaller surgery is often perfectly sufficient. In contrast, for atypical carcinoid tumors one sometimes needs to be more aggressive with a more standard cancer surgery. Sometimes we'll even think about post-operative treatment with radiation or chemotherapy to try to improve the chances of cure.

What we'll do now is move down that GI tract, to the small intestine. One feature of small intestinal carcinoids is that the tumor itself is actually within the muscle wall of the intestine. This makes it very, very difficult to see. One can do colonoscopies, looking at the small intestine, and completely miss this sort of tumor. One can even do radiologic studies called small bowel follow-throughs, that will look completely normal precisely because the tumor is hiding deep down within that muscle wall.

Another characteristic is that the tumor itself can cause a bit of a bend in the small intestine. People who have these tumors frequently will have long-standing, sometimes yearlong symptoms of intermittent abdominal pain because of intermittent small bowel obstruction. In addition to this intermittent small bowel obstruction, small intestine carcinoids can often be associated with fibrosis or thickening and scarring of the small intestine, and ischemia, which is lack of blood flow. This can also cause severe abdominal pain, and sometimes even be life-threatening. Because of these symptoms, even in people who may already have liver metastases, or metastases to other sites, we will very often recommend removing the primary small intestine carcinoid with what's called a palliative resection to help improve some of these symptoms.

Moving further down the gastrointestinal tract, we come to the appendix. Appendiceal carcinoids are actually the most common tumor of the appendix. In contrast to tumors of the small intestine and bronchial carcinoid tumors, appendiceal carcinoids frequently occur in younger people, often in their thirties and forties. They are most often found by accident in people who are having appendectomy for acute appendicitis. We know a fair bit about how to manage appendiceal carcinoid tumors. What we know comes primarily from a very large study done by one of the pioneers in carcinoid research, Charles Moertel, who published almost twenty years ago. What Moertel did is looked at over one hundred people who had been diagnosed with appendiceal carcinoid tumors and looked at what happened to them. He found that people who had undergone removal of a small appendiceal carcinoid tumor, less than two centimeters in diameter, never had metastatic disease. In contrast, people who have larger appendiceal carcinoid tumors, measuring two to three centimeters, had metastases 20% to 25% of the time. And people who had really big tumors, more than three centimeters, actually had metastases 45% of the time. So based on this information, we know that if people have an appendiceal carcinoid measuring less than two centimeters, they are going to do just fine by having the appendix removed with a simple appendectomy. People who have larger appendiceal carcinoid tumors should usually have a larger, more typical cancer operation with a right hemicolectomy that removes any associated lymph nodes.

The rectum is not an uncommon spot for carcinoid tumors to occur. Carcinoid tumors comprise about one to two percent of all rectal tumors. They are again more common in older individuals, over 50 years of age. They are being found more and more commonly these days as people are getting screening colonoscopies. They are often found, again, completely by accident. Very much like appendiceal carcinoid tumors, the management of rectal carcinoid tumors is based on the size of the tumor. People who have smaller rectal carcinoid tumors, less than two centimeters, can do just fine with a local excision, a small operation to remove the tumor. Metastases are very infrequent. In contrast, people who have larger tumors measuring more than two centimeters in size, generally need to have a larger cancer operation.

We all hope that when someone is diagnosed with a localized carcinoid tumor in the lung, or the small intestine, or in the rectum, that it can be removed surgically and that it will never ever come back. Unfortunately we know that this is not always the case, and sometimes we are faced with metastatic carcinoid tumors. One of the most common symptoms associated with metastatic carcinoid tumors is, of course, the carcinoid Syndrome, which classically is manifested by intermittent flushing, frequent watery diarrhea, and less commonly symptoms of breathing difficulties like asthma.

One of the big success stories in managing carcinoid tumors was the discovery of octreotide. It was found that octreotide, or Sandostatin, can be extremely effective in controlling this syndrome. There have been some changes over the past few years in how octreotide is given. Generally what we do these days is start people initially on short-acting or subcutaneous octreotide at a dose about 150 mcg three times a day. If people respond to that, and if people do not have any adverse reaction, we will then rapidly convert them over to the long-acting form of octreotide, or octreotide LAR, usually starting at a dose of 20 mg given by intramuscular injection every four weeks. In cases where the 20 mg dose is not sufficient, we will escalate to 30 mg and sometimes even to 40 mg given every four weeks to best control symptoms.

Octreotide is very similar to a naturally occurring hormone in the body called somatostatin. Carcinoid tumors, as well as other endocrine tumors, express a very high number of receptors for human somatostatin. About 90% of these tumors will express somatostatin receptors. What octreotide does

is simply search out those receptors on the cancer cells, bind to them, and shut down the carcinoid tumor cells, preventing the secretion of hormones.

There is another interesting application for octreotide. If one attaches a radioactive label to octreotide, it will take that radioactive label right to the tumors. And when you do a scan in that situation, you have what's called an octreotide scan. These scans can be quite useful in detecting metastatic disease, especially when it might not be that easily detected with standard imaging modalities like CT or MRI scans.

More and more, in terms of following patients with carcinoid tumors and other neuroendocrine tumors, we're using biochemical markers. The classic marker is, of course, the 24-hour urine collection for 5HIAA. 5HIAA is a metabolite of serotonin, one of the most common hormones secreted by carcinoid tumors. One of the problems is that not all patients with metastatic carcinoid have the carcinoid syndrome and secrete serotonin. For example, patients with bronchial carcinoids or rectal carcinoids will not have high levels of 5HIAA. Similarly, patients who have metastatic pancreatic endocrine tumors also won't have high levels of 5HIAA. In such patients, it is better to use another tumor marker called chromogranin A. This can be done just with a blood test, and is useful not only in patients who have the carcinoid syndrome, but also in patients who have carcinoids that are not secreting serotonin and in patients with pancreatic endocrine tumors.

Many patients will do extremely well with octreotide alone, sometimes for many years, experiencing no symptoms whatsoever. The challenge comes in people who are breaking through the octreotide and who are still having symptoms despite maximal doses. One consideration in such patients is alpha interferon, a drug that has been studied most in Sweden but has also been used in this country. We know from European studies that treatment with alpha interferon can decrease urinary 5HIAA levels in about 40% of patients. Actually getting tumor shrinkage is less common. One reason that Interferon is not more widely used in this country is that it can be associated with side effects. Sometimes patients may experience depression and decreases in blood counts associated with the drug, so it's not necessarily for everyone.

Increasingly, as people are living longer and better lives, we're actually faced with another complication. This is a late complication of carcinoid syndrome called carcinoid heart disease. With carcinoid heart disease one sees a retraction of the heart valve leaflets, associated with valve thickening. And this makes the valve leaky and, ultimately, what can happen is that patients can get what's called right heart failure, with the heart becoming very inefficient. An option for such patients is a valve replacement, to fix the leaky heart valve. In the older studies valve replacement was associated with relatively high complication rates. In recent years, these surgeries have become much more successful and, in fact, we know that patients who do undergo a successful valve replacement can have significant improvement in symptoms of right-sided heart failure. In properly selected patients, it is certainly something that should be considered.

Another question that comes up in patients with metastatic neuroendocrine tumors is how best to manage liver metastases. The liver is probably the most common site for carcinoid and other neuroendocrine tumors to metastasize. There are several options that are generally considered to treat liver metastases in patients with neuroendocrine tumors. The first of these is hepatic resection, or cutting out the tumors surgically. The second is liver transplantation. And the third is hepatic artery occlusion, or chemoembolization.

Hepatic resection is probably the first option and in some ways it's the best option in the right patients. In one surgical series, published just a few years ago, it turned out that patients who were getting resection or removal of their liver tumors surgically, had four year survival rates that were really quite good - 70-80%. Even more impressive is that almost 90% of these patients had relief of symptoms of flushing and diarrhea from their carcinoid syndrome.

The problem, of course, is that not every single patient is going to be able to undergo complete removal of all the tumors surgically. This brings up of liver transplantation. Liver transplantation is a big deal. If you look at overall survival of patients who have had liver transplantation for neuroendocrine tumors, especially for carcinoid tumors, it's actually quite good. The difficulty comes when you look at disease-free survival, patients who are actually living without evidence of any

carcinoid tumor. Here the story is somewhat less encouraging, with less than half of patients actually being cured of their disease. So patients can live a long time with transplantation, but, frankly, these days patients are also living a long time without liver transplantation. The question is, is liver transplantation really worth it if a large proportion of patients are actually going to end up with recurrence. The additional difficulty in this country is that liver transplantation is not easily available. So while liver transplantation can be considered in very selected patients, it's certainly not routine.

Something that is far more commonly done, and perhaps more applicable to most patients is chemoembolization. Most studies clearly indicate that this procedure can help patients who have liver metastases. Again, one of the most important series was done by Moertel about ten years ago, and demonstrated high response rates. The challenge and difficulty is that the duration of response was not all that long. Patients had improvement in symptoms, decreases in tumor size that lasted about six months. After that, they may have needed another chemoembolization or needed to go on to another form of therapy. So it's not perfect, but it certainly can help.

There was another interesting observation in this particular study, which was that when systemic chemotherapy was added after chemoembolization, the response rates increased to 81% and that the duration of response, the length of time that patients were responding, seemed to increase dramatically to almost 20 months. This raises the other big question in the treatment of patients with metastatic neuroendocrine tumors, and that question is what exactly is the role of systemic chemotherapy in this disease? It's not a very easy question to answer. There's a long history with chemotherapy in patients with metastatic carcinoid tumors that dates back all the way to the 1970's. In an initial study patients underwent a randomization to receive either a combination of streptozocin and 5FU, two chemotherapy drugs, or another combination of streptozocin and cytoxan. The response rate with streptozocin 5FU was 33%. There were two problems. Number one, if you look a median survival, it does not look particularly encouraging. In addition, the chemotherapy was relatively toxic. In a second trial, the streptozocin and 5FU regimen was changed slightly to improve the side effect profile. There were lower rates of toxicity, but the response rates also decreased to 23%. Based on this data, many physicians feel that there may be selected patients that benefit from some of these systemic chemotherapies. However, none would necessarily be considered a "standard" treatment for all patients with metastatic carcinoid tumors.

There is a perception that, for patients who have pancreatic islet cell tumors, systemic chemotherapy may be somewhat more effective. One trial in fact reported a 69% response rate with a regimen that combined streptozocin and doxorubicin. This seems quite encouraging; however the criteria used for response are not the criteria that we're using these days. In more recent experiences, one at Memorial Sloan Kettering Cancer Center, and one at our own institution, Dana Farber Cancer Institute, the true response rate was reported to be less than 10%. This is not to say that this chemotherapy is not without merit or without benefit. However, it's probably not accurate to expect that with this chemotherapy regimen the tumors are simply going to dissolve away.

I think most people would agree that the experience with the older chemotherapy regimens is somewhat mixed. There is obviously great interest in finding new forms of therapy that are going to be more successful and less toxic than some of these older regimens which, in truth, really date back all the way to the 1970's. One form of therapy that is certainly being explored utilizes targeted radiotherapy with somatostatin analogs. If one attaches a radioactive isotope to octreotide, one can carry the radioactive particle right to the tumor. This strategy has been looked at with a variety of different radioactive isotopes. The isotope where there's probably been the most experience so far is yttrium labeled octreotide. One can clearly get some tumors to shrink with these sorts of therapies; however, one of the complications of this type of therapy is, again, toxicity. One difficulty has been renal toxicity which has limited the amount of treatment that patients can actually get. This is an area that is still being actively worked on, and there continues to be excitement about new variations on this strategy.

Another approach has been to find new chemotherapy agents that may have more activity, and may have less toxicity than some of the older agents. We have to date looked at a variety of some of these newer chemotherapy agents, with mixed results. The first of these was an agent called Taxotere. Taxotere is a chemotherapy that has actually been widely used and very successful in patients who have metastatic breast cancer, as well as other malignancies. Of 21 carcinoid patients

treated with Taxotere, two had minor responses. However, we had no really impressive tumor shrinkage, leading us to try to pursue other types of treatment. Another drug that we looked at is gemcitabine. Gemcitabine generally is very well tolerated and is widely used in treatment of patients with pancreatic cancer. Unfortunately, our experience here was also not particularly positive and we actually saw very little activity in patients with neuroendocrine tumors.

Over the past two years, there has been a revolution in cancer treatment with the emergence of many so-called biologic therapies. These therapies are targeted therapies that don't attack the good cells, the way standard chemotherapy does. They, instead, try to target some of the specific biological processes that are important for cancer cell growth. One of the first biologic therapies was Endostatin, which was developed and discovered by Judah Folkman Children's Hospital in Boston. Endostatin is really a naturally occurring molecule within most animals. It was found that Endostatin seemed to inhibit blood vessel formation, targeting endothelial cells, or cells that reside on the inside of blood vessels. Many people thought that Endostatin was going to be the answer and was going to make all cancers simply dissolve away and that we'd never have to worry about chemotherapy again. Amidst this excitement, true clinical trials were undertaken, one at Dana Farber, another one at M. B. Anderson, trying to find what the right dose of Endostatin would be. It turned out that that one patient on these trials was a patient with a neuroendocrine tumor. The patient had been experiencing progression of their disease prior to initiation of therapy; after getting treated with Endostatin, they had a tumor reduction of 17%, a reduction that lasted eleven months.

Based on the results of that one patient responding to Endostatin, Endostatin was taken into a Phase II study, specifically for patients with neuroendocrine tumors. The study is still ongoing. So far, 41 patients have been enrolled. Some of us who were expecting Endostatin to completely eliminate or dissolve tumors, were disappointed. It turned out that 2 out of 37 patients had minor radiologic responses, experiencing some degree, but not dramatic shrinkage of their tumors. What has been interesting is that 62% of these patients actually had stable disease over a prolonged period of time. It will be interesting, as these patients continue to receive treatment, to see what happens down the road and to determine what long term effects Endostatin may have for patients with metastatic neuroendocrine tumors.

Now certainly for some patients, especially patients who have more aggressive tumors, or who are already very symptomatic from their tumors, just having prolonged stable disease may not really be what they need. Some patients clearly need decreases in the volume of tumor. They need some of those tumor cells to be killed off. We have continued to try to find new combinations of treatments that can help achieve that.

There is an old chemotherapy drug that is sometimes overlooked in the treatment of patients with neuroendocrine tumors. This is a drug called DTIC. DTIC has been looked at in fairly large trials, one in carcinoid tumor patients, and one in pancreatic islet cell tumor patients. In carcinoid patients, DTIC resulted in responses in 16% of patients and, in pancreatic islet cell tumors, the response rate was somewhat more encouraging at 33%. The problem with DTIC, as with many of these older chemotherapy drugs, can be that some patients will have side effects. This side effect profile has prevented the more common use of DTIC in patients with these tumor types. Over the past several years there has been the development of a newer drug, essentially an oral form of DTIC called Temodar. It works in very much the same way as DTIC, but instead of having IV infusions, it can be taken in pill form. It also has an improved toxicity profile.

Another drug, thalidomide, has recently been used together with Temodar. Thalidomide actually became infamous in the 1960's for causing birth defects. One theory is that thalidomide may inhibit blood vessel formation, and, for that reason, may have some benefit as an anti-cancer agent. Combinations of thalidomide and Temodar have been looked at and have been successful in recent clinical trials with brain tumors. Thalidomide by itself also has activity in a relatively rare hematological malignancy called multiple myeloma

Based on some of these early results, we have actually recently evaluated a combination of Temodar and thalidomide, in people who have neuroendocrine tumors. We have seen some encouraging preliminary results with this combination, including a relatively high number of chromogranin A responses as well as some actual radiologic tumor responses.

There has been a lot of publicity and a lot of excitement, particularly among physicians, but also among patients, regarding a whole new family of targeted cancer treatments. This story really began with a very rare type of tumor called a GIST, or a gastrointestinal stromal tumor. Not unlike neuroendocrine tumors, these GIST tumors had a long history of being very, very difficult to treat with standard sorts of chemotherapy.

Over the past several years, a new drug called Glebec was developed. Initially, one patient with GIST was treated with Gleevec and had a dramatic tumor response. This caused huge excitement because by taking this small pill once a day over the course of just four weeks, these tumors almost immediately shrank dramatically. The way Gleevec works is actually by specifically targeting a cell surface receptor. In the cancer cell, this receptor is activated. And as it's activated, it activates a whole host of other proteins within the cell. Those proteins then tell the cell to start dividing. Gleevec blocks the communication between the receptor and the rest of the cell. By blocking this growth signal, the cells not only to stop growing but also to die off.

It's important, though, to remember that Gleevec works on a very specific receptor-the C-kit receptor, which is only one of a very large family of growth factor receptors that are arrayed on these surfaces of a variety of different tumor cells. These receptors can really be categorized into several different groups, and there's one group that actually may be of particular interest to patients who have carcinoid and other neuroendocrine tumors. These receptors include a receptor called the PDGF, or platelet derived growth factor receptor, as well as another receptor called the VEGF, or vascular endothelial growth factor receptor. These two receptors are thought to be particularly important in the development of blood vessels. Several drugs that block the VEGF receptor have now been developed. One of these drugs, called SU011248 resulted in responses in patients with carcinoid tumors in an early phase I study and is currently being evaluated in a national phase II study for patients with metastatic neuroendocrine tumors.

I'll summarize by saying that at this time surgery alone still remains I think the mainstay of management for patients with neuroendocrine tumors. In patients with metastatic neuroendocrine tumors, the use of octreotide has offered significant benefit in the treatment of hormonal symptoms. Traditional chemotherapy may have a specific role in certain patients, but we'd certainly like to do better. New targeted agents, some of which may specifically target blood vessel formation, have shown some promise in early trials, and continue to be evaluated in clinical trials for patients with neuroendocrine tumors.

End of Lectures

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Question & Answer Period

Questions Posed By Audience Members

MNYCSG meeting April 27, 2003; The Dana Farber Experience

Question:

Concerning clinical trials, would you only submit a patient for such trials if standard therapies have been used and failed?

Dr. Kulke: One of the difficulties, or challenges I should say, with Carcinoid is that there aren't a

whole lot of standard therapies. The only really standard therapy would be Sandostatin. It's not to say that there aren't any treatments for Carcinoid. And I hope I've displayed that there is a whole range of different types of treatments for Carcinoid tumors. And I think the challenge is finding the right type of treatment for each specific patient. And there are certainly some patients for whom surgery or embolization chemotherapy might be appropriate, and other patients for whom clinical trials might be appropriate. That's why I think that's just a decision that needs to be made on an individual basis.

Dr. Warner: I think your answer is going to be the same for the next question, which is:

Question:

How does a newly diagnosed patient decide what's best?

Dr. Warner: I think each decision really does need to be individualized in the absence of any truly uniform standard treatment for Carcinoid. But there are lots of options out there for every patient.

Question:

Which is better, hepatic artery embolization (bland embolization) vs. hepatic artery chemoembolization (HACE)?

Dr. Warner: The next question here is regarding hepatic artery embolus injection vs. hepatic artery chemo-embolus injection. I have strong opinions about this. I'll let you answer it first.

Dr. Kulke: If I understand the question correctly, there is an older technique called portal artery occlusion, where they actually tied up the whole artery to the liver. And the theory here is that the tumors get their blood supply from the artery and the normal liver gets most of its blood supply from actually the portal vein. So this is a way to selectively kill off tumor cells. I think in recent years that this sort of very crude approach of tying off the entire artery has been abandoned. I think most people now use chemo-embolization, which is a somewhat more specific way to get individual lesions. (I hope I answered this right.)

Dr. Warner: Well, we all agree, everybody now, that surgical ligation of the main branch to the artery to the liver is not going to be effective because very rapidly new branches form beyond the point you've tied off the vessel and within 24 hours it's not effective. So that doesn't count. But the question is whether to just inject bland embolus material particles or whether to mix chemotherapy agents with it. There are a few centers that still prefer to do just the bland embolus. By doing that, there are fewer side effects and the results are just as good. But most of the centers where a lot of this work is done now feel that chemo-embolus is preferable. We agree the side effects may be somewhat greater, but they are temporary and they are usually, almost always, tolerable. The durability of the response is better with the chemo-embolus. That is to say they both cause a good response, but it lasts about twice as long or even longer if you have the chemo mixed in with it. So I'm strongly in favor of the chemo mixed with the embo.

Question:

What would be the right procedure for treating a metastatic non-functioning Carcinoid involving the liver?

Dr. Kulke: Well, that's an individual call because there are many ways this can be handled. Without going into the details of tumor size, distribution, how many, and other characteristics of the individual tumor cells, you can't make a generalization. This, like so many other things in the treatment of these patients, has to be customized to their specific technical needs.

Question:

What is the reason for taking niacin or other nutrient supplements?

Dr. Warner: The tumor that manufactures serotonin, even if it doesn't cause the Carcinoid Syndrome, has to take the raw material which it converts into serotonin, and that raw material is the amino acid tryptophan. Tryptophan is an essential amino acid that you can get only from your diet. Your body can't make it. And tryptophan serves in the normal body's function a number of purposes. It makes

other things besides serotonin. Normally only 1% of it goes to make serotonin and the majority of it goes to make protein that makes muscle, and also niacin, which is an essential component of the B complex. A deficiency of niacin is known as the disease Pellagra. Pellagra, which was well known during World War II in prisoners of war who were starved, is characterized by three things: diarrhea, horrible skin rash, particularly when exposed to sun, and mental changes. The three D's: diarrhea, dermatitis and dementia. Now, a patient with Carcinoid Syndrome, or even without the syndrome, doesn't want to have those features superimposed upon his Carcinoid symptoms. And, actually, sub-clinical Pellagra may be present in patients who are deficient in this substance. So, the addition of niacin to supplement the diet is a very good measure that should be done in all such patients.

Question:

What tests to monitor LC NEC, (presumably meaning large cell Neuroendocrine cancer) should be done after successful surgery has been done removing such a tumor from the right upper lobe of the lung? (In other words, I presume this means x-rays, chemical tests, etc.) What would you be doing?

Dr. Kulke: I think the large cell neuroendocrine carcinoma falls more in that subcategory of the atypical Carcinoid tumors. Two things about those; One is that they are more aggressive than the typical ones and also actually respond better to chemotherapy. And so I think that this sort of person should be followed regularly with many of the classic tests that are used to follow any cancer patients: cat scans, in particular I think would be important, as well as routine follow-up visits. These more aggressive forms of Carcinoid sometimes do make chromogranin but probably not quite as predictably as the more typical ones. So I'm not quite sure how reliable tumor markers would be in that particular case.

Dr. Warner: Let me add something to that. I think it's useful in all cases regardless of what category of Carcinoid or Neuroendocrine tumor it may be to at some time in their course do a full panel of all of the usual neuroendocrine tumor markers, especially when there is still tumor present. This is why we like to do these tests before surgery. So we then know what marker or markers are going to be increased by that particular tumor and what is best to follow subsequently. There are some uncommon markers that are sometimes useful and occasionally the only ones that can be measured and followed. For example, the Alpha sub-unit of human Chorionic Gonadotropin is sometimes positive, sometimes the Beta sub-unit in rectal Carcinoids. And it may be the only thing that you can follow. I just mention that are others also that can be followed in this instance. So, again, every patient has to really have a thorough evaluation.

Question:

After surgery for Carcinoid of the liver, to which it has spread from the small intestine, the patient notes that the surgeon doesn't want to go back and operate again, but rather to give Sandostatin.

Dr. Warner: Well, that may be appropriate. I don't think we can answer that without knowing more details.

Question:

As I was originally diagnosed with Carcinoma and then re-diagnosed with Carcinoid a number of times and, finally, Neuroendocrine Carcinoma, which is really a more malignant Carcinoid, what is the problem if chemotherapy is ineffective, why should it be given at all?

Dr. Warner: I'd like to share in this answer with you. It is a general rule that the more aggressive the Neuroendocrine tumor is in terms of being more like an ordinary cancer in terms of its rate of growth and microscopic appearances, the only good thing about it is the likelihood of a response to one of the more aggressive chemotherapy routines increases such as, Cisplatin, P16, which Dr. Mortell had shown about a decade and a half ago, and which you illustrated.

Dr. Kulke: Absolutely. I think this question actually brings up two issues. One is the issue of having been originally diagnosed with one kind of tumor and then coming back later and saying it's a Carcinoid tumor, which is actually not uncommon. I think it does go back to the fact that Carcinoid tumors certainly in some places are not seen very frequently. And I do think it is often useful to have the pathology of those biopsies reviewed at some place that sees a fair number of Carcinoids so that one can be sure of the diagnosis. And the other question, of course, gets back to the chemotherapy

which, again, for these aggressive forms of Carcinoid probably should be the first option because in some cases it really can be very effective in these more aggressive forms. In the less aggressive, the more typical cases, the whole issue of chemotherapy I think is more controversial. I know we were talking about that. And I think at the very least we should not necessarily expect chemotherapy at high doses to shrink these tumors away like they do in some other forms of cancer. That's not to say, though, because in some cases chemotherapy can be helpful in at least stabilizing the disease and helping control some of the symptoms in the right patients.

Question:

What markers and or growth factors are known to be present in gastrinoma or other islet cell tumors that SU011248 could target? In other words, what are the particular markers that you could stain for that would predict the possibility of likely response?

Dr. Kulke: There's actually very little known about that. And it's actually a very interesting story when we think about drug development. We often think about people understanding the biology of the tumors and then developing a drug to try to treat it. In this case, it almost seems that things have worked backwards. It was almost by accident that responses were seen in Carcinoid tumors. So we really don't know the answer to that question. We do know, at least in some small studies, that Carcinoid tumors do have high levels of both the vega-vascular endothelial growth factor in PDGF, which is targeted by SU11248. It would certainly say that the whole reason for doing the clinical trial is to see if that pans out and, in fact, one aspect of this trial is to try to actually get biopsies to assess if those targets are really there. So it is very much unknown right now.

Question:

Dr. Warner: Are you staining the tissues of these trial patients for those markers to see if the findings correlate with the results?

Dr. Kulke: Absolutely. It's actually an absolutely critical part of this trial, and biopsies are in fact required in order to go on to the trial if they can be obtained for precisely that reason. This is a very critical thing to understand and, frankly, even if the 11248 does not work in some patients, there may be some useful information that comes out of it in terms of what other targets might be useful for future studies.

Dr. Warner: Epidermal growth factor, platelet derived growth factor, and some of these other growth factors that you heard mentioned, are available commercially to be used for staining biopsy specimens. So as soon as the results of this study are available, I believe if they're favorable, the possibility of rather rapid activation of this whole form of treatment would exist.

Question:

If you want to be part of a clinical trial, how do you do it? Does your doctor have to recommend you, or what steps should be taken?

Dr. Kulke: The issue of clinical trials I think really needs to be a partnership between the patient and the physician. I have to say that I think the patients who have participated and are participating in clinical trials are incredibly courageous and really should be the ones that are getting all the credit for any of the successes because it's a brave thing to do. It's impossible for any physician to recommend a clinical trial in the sense that they can't say that I think that this drug is going to work for you, this is the right thing to do. Because, by its very nature, the results of clinical trials are unpredictable and I think I showed you initial trials that were not positive as well as some positive results. So it needs to be partnership.

Question:

What is the preliminary safety data of SU011248?

Dr. Kulke: There are a total of about 150 patients worldwide that have now been treated with SU11248. Not with Carcinoid, primarily with these gist tumors, the rare form of Sarcoma. It's actually been successful in treating patients where the Gleevec was no longer working. In general, it seems to be quite well tolerated. Again, it's a pill. There are as part of all of these trials, a very strict safety monitoring. Some side effects have included effects on blood counts. There have also been some

indications of effects on muscles, including heart muscles. So people are getting very closely monitored with either echocardiograms or other ways to monitor heart function on the trial.

Question:

Dr. Warner: You didn't mention clinical trials with Epoprostenol, which are being done in various institutions. I wonder if you can say anything about that?

Dr. Kulke: I don't have any information on those.

Question:

Dr. Warner: A question is posed here about the Endostatin trial. What was the progression rate among patients prior to their treatment in the trial? In other words, were they all aggressive tumors or what?

Dr. Kulke: I think that's something that we very much would have liked to have had. It is difficult to assess and we do not have that information. One of the challenges is that people coming in will have had CAT scans at very different sorts of intervals so it's very difficult to have a uniform sense of what the progression rate was. I think it's fair to say that there was a mix. Within the trial, some people had had a fairly indolent stable disease, whereas other people had had more aggressive types of Carcinoid.

Question:

Dr. Warner: The next questioner poses two questions. The first of which perhaps you can easily answer. They want to know where the SUO11248 study is being done?

Dr. Kulke: Well, we know where it's being done.; There are five sites actually. One is Dana Farber, Fox Chase Cancer Center in Philadelphia, University of Alabama, Mayo Clinic and University of California San Francisco

Question:

Dr. Warner: And, do we know when the study will be completed in these different centers?

Dr. Kulke: It's just started; we don't know when it will be done.

Question:

What about radiofrequency ablation results? How effective, and when indicated?

Dr. Warner: Well, that's a big question. This technique of radiofrequency ablation has been around now for a number of years and the medical literature has many articles with reports of its safety, of its efficacy, of the indications when it should be done, and so on. It varies depending upon the size of the tumors, the number of tumors, the technique used - there are different machines that are used for this ablation. But, by and large, with appropriate choice of tumors, the results have been very good. However, you can't do a whole liver full of tumors at one sitting, nor can you do tumors that are beyond a certain size. So there are limitations. But within the parameters that are permitted for the treatment, the results are very good, again, though, it has to be remembered, it's only one modality. And the best way, at least in my view of treating patients with this disease, is the sequential application of multiple modalities with the timing being properly chosen. In other words, it's not just one treatment you can give and then you're done- you're either better or you're not. You've got to keep after it. And, if you do, then you'll get a good response.

Question:

Should Carcinoid patients avoid foods high in serotonin?

Dr. Kulke: I may have somewhat of a radical philosophy, but I think the goal should be - get an effective treatment so you can eat whatever you want.

Dr. Warner: I agree with that entirely. The only purpose to avoid the high serotonin-containing foods is when you're going to have a 24-hour urine 5HIA test, and then it's only for the test. Otherwise, it's not necessary.

Question:

Is anyone looking at Carcinoid cells at the genetic level to determine better treatments?

Dr. Kulke: I would say yes. Especially with the evolution of some of the availability of some of these very targeted treatments, treatments that are targeting specific molecules, there's a huge interest in doing exactly that. And those sorts of analyses are part of the trial of SU11248, but are actually part of a much broader effort to find new targets and better targets for treatment.

Dr. Warner: There even are some plans on the drawing board for utilizing genetic mechanisms in the treatment of Carcinoid. That is just as colon cancer metastases are being treated with the implantation of genes, or of viruses that are lethal to the colon cancer cells by getting at their genes, similarly such plans are being prepared for Carcinoid. It's not up the clinical utilizable level yet, but it has certainly not escaped consideration.

Question:

Dr. Warner: The next question here is for you regarding DTIC. The question is: What were the two death scores by renal toxicity? And also what toxicity has been developed or shown up with thalidomide Temodar?

Dr. Kulke: I don't recall exactly in the DTIC trial what the deaths were due to. I think there is an issue of exactly how the DTIC is given. In some of these older trials, it was given at very high doses, which works very well for people with highly chemo responsive tumors, like lymphomas. But it may not be right approach for patients who have slower growing tumors like Carcinoid. And certainly given at different intervals, and perhaps more modest doses, DTIC is significantly less toxic. Regarding the trial, I think we don't have final toxicity data on Temodar and thalidomide at this point. I would say, in general, it's been reasonably well tolerated. Some rashes. We've not yet seen a significant suppression of blood counts, significant infections, and things like that. So, in general, it seems to be reasonably well tolerated.

Question:

Is Carcinoid a hereditary disease?

Dr. Warner: 4% of all Carcinoids are proven to be genetically determined and are hereditary. They're transmissible from one generation to the next. That's only 4%. And a certain percentage of that 4% are part of the MEN syndrome, a certain percentage are outside the MEN syndrome, but are truly hereditary. This means that hereditary Carcinoid is very, very rare. And almost always there's an obvious family history. If you're the only one in your family that you know of or that you can find out of, who has this disease, it's exceedingly unlikely that it's a hereditary disease that can be transmitted to your offspring. If you know that an uncle, a grandparent, or even a closer relative, had Carcinoid, it makes it a very strong possibility that it is hereditary and appropriate studies are required.

Question:

Dr. Warner: The next question concerns Octreotide LAR, and it says - When it's given up to 40 mgs, is that a new dose? Because all the information that this questioner has is that 30 mgs is the highest dose. Do you ever use larger than 30 mgs doses?

Dr. Kulke: We go up to 40, which is two of the 20 mg injections, one in each cheek. We haven't gone up beyond that. I think more for practical reasons than anything else.

Dr. Warner: I use up to 60; 30 mgs on each side, and that isn't really an excessive amount. In appropriate patients, that will be helpful, where lower doses won't be. Furthermore, trials are underway where an experimental variety of Octreotide LAR using one shot of 160 mgs is being done in Europe, and I think somewhere in this country, because it's been shown that the larger doses of this drug have some more effective anti-tumor action. So it's being utilized for its tumor-inhibiting properties in that trial. But there's certainly no harm to give 60 mgs or 50, it's just that there may be economic considerations because it is very expensive.

Question:

Dr. Warner: Here's a question which we'll answer I believe only in a general sense because it's case specific, but it does have some general application.

My doctor recommends that I can have radiofrequency ablation, removal of the gall bladder and removal of the original tumor (presumably the primary tumor) all at one time. My surgeon says no. Doing radiofrequency ablation is enough. They'll do the others a month later. What is our opinion?

Dr. Kulke: Again, every case is very individual. A lot of these decisions are technical and depend specifically on the location of the tumors, what the surgeon is comfortable doing. I would say, frankly, we generally defer to the surgeons on questions like this because they are really often of a technical nature.

Dr. Warner: That's right. It's a matter of whether the surgeon can get into that abdomen with ease and do all of this without undue complication or problem. If so, then, of course, it's desirable to do it all at one sitting. In fact, it's almost a dictum, at least in our practice, that when a patient with Carcinoid has an operation for any purpose and the abdomen is entered, if that patient is taking Octreotide (Sandostatin), or is likely to be treated with it for a long time in the future, then, unless it complicates the surgery excessively, the gall bladder ought to be removed always because it precludes future development of gall stones (which can happen in up to 50% of the cases). Not that everybody with gallstones develops symptoms, but a significant proportion does, and it avoids that problem. Do you share in that feeling?

Dr. Kulke: I do, absolutely.

Question:

Dr. Warner: The response rate seems to be approximately 33%. (I presume that means the response rate to chemotherapy.) Is this a typical percent of response for treatment modalities? (I presume that means all modalities.) And then, finally: Regarding tumor growth after chemo embolization, do tumors grow faster thereafter? This is a separate question. I think we can address both.

Dr. Kulke: I think the response rate of chemotherapy, which I think often is in the 20 to 30% range for Neuroendocrine tumors, is probably somewhat lower than we would like to see. There are other types of cancers that are far more chemotherapy responsive, with response rates up 50%, 70%. At the same time, there are tumors for which chemotherapy is standard used where response rate is only about 8 or 10%. Pancreatic cancer is one example of that. So I think the issue is really, again, individual. Is the chemotherapy really going to help from a clinical standpoint? We need to balance what the chemotherapy regimen is, what the side effects are, with that potential response rate with that potential benefit. And I think it's different for everybody.

Dr. Warner: As an addition to those comments, I would ask you the following. We have, as you all heard, a variety of chemotherapy drugs available. The best in general for the average case is about a 33% chance of a beneficial response. But does that mean if a patient fails to respond to one drug, they are predestined to not respond to a trial with another drug? Or, does the slate get wiped clean and they have another 33% chance with the next drug?

Dr. Kulke: I don't think we know the answer to that with statistical certainty. But certainly it is not the cases that if the first treatment doesn't work that you're not going to have success with another treatment. I wish that we were able to predict with 100% certainty which treatment would work for which patients. The truth is though that right now we're not quite smart enough to do that. You try. You give it your best shot the first time. If that doesn't work, you try a second time, a third time, a fourth time. There are a variety of different types of treatment, not just chemotherapy, as we've been discussing, that can be used, and you just want to keep on going.

Dr. Warner: As some of you know, I've been using when it's possible, an older technique that's been somewhat abandoned for ordinary cancers, but I've found it be helpful with Carcinoids and Neuroendocrine tumors; namely, to get a specimen of the tumor and submit it for cell culture drug resistance testing. That is, growing it or harvesting the tumor cells and growing them, or at least keeping them alive in a test tube. And then testing samples of these cells against different chemotherapy agents to see, at least in the test tube, what drugs these tumors will be most

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responsive to, and then choosing one of those drugs for actual clinical use. This technique has been around for at least twenty years and at first looked very promising for more common cancers like colon and breast cancer, for example, but never really proved to fulfill the promise that it held. However, in the last three or four years, using it for Carcinoids, it has proven to be more helpful. And so I find it potentially useful and it may be an answer. But, of course, it has to be used more and some statistical conclusions derived. It's not widely used because it's expensive.

Dr. Warner: Are there any questions from the floor that we can field?

Question:

Is it the histology alone that determines if a tumor is atypical versus typical and whether it's of an aggressive nature and responsive to chemotherapy? Do you just use the histology, or is it also dependent on the course of the disease?

Dr. Kulke: I think the histology is probably the best first indicator that we have. So we could look very specifically, for example, at the number of mitosis, the number of cell divisions. And one commonly used criterion is the number of cell divisions per ten high-powered microscopic fields. And if it's less than one, that is generally a very low growing or typical Carcinoid. If it's higher than that, it may be atypical. That being said, that histologic review is not always 100%, and sometimes you can be fooled. And, ultimately, it is the clinical course that is going to tell you what exactly this tumor is going to do.

Dr. Warner: I'll add to that. Though the histology is the initial way, there may be a sampling error. Particularly, if it's a needle biopsy, since within the same tumor, there will be different degrees of malignancy and so a sample may not represent what's going on throughout the entire tumor.

Thank you very much.

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