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### Heated Intraperitoneal Chemotherapy (HIPEC) for Advanced Abdominal Cancers

Narrator:

Welcome to “Medical Breakthroughs” from Penn Medicine, Advancing Medicine Through Precision Diagnostics and Novel Therapies. Your host is Dr. Lee Freedman.

Dr. Freedman:

Hyperthermic intraperitoneal chemotherapy, or HIPEC, is one of the most innovative treatments available today for complex abdominal cancers. What is it? Who is a candidate, and what are the outcomes?

I am your host, Dr. Lee Freedman, and with me today is Dr. Giorgos Karakousis, Assistant Professor of Surgery at the Hospital of the University of Pennsylvania. Dr. Karakousis, thank you for being with us.

Dr. Karakousis:

Thank you for having me.

Dr. Freedman:

Well, it is our pleasure and this is something I know nothing about. Can you please just tell us what exactly is hyperthermic intraperitoneal chemotherapy?

Dr. Karakousis:

So, hyperthermic intraperitoneal chemotherapy, or HIPEC, is a procedure which involves infusing the peritoneal cavity in patients with advanced peritoneal surface malignancies with high-dose chemotherapy. And typically, this procedure is done in conjunction with what is called cytoreductive surgery, or tumor debulking surgery, where the gross or macroscopic tumor is removed first, followed by this chemo infusion into the abdominal cavity.

Dr. Freedman:

Fascinating, and I would think intraperitoneal is done to reduce side effects or increase efficacy?

Dr. Karakousis:

It's a combination of both. Carcinomatosis historically has had poor outcomes in patients, and part of the thought behind that is that systemic therapies may not reach the peritoneum as well as direct therapy. And so, the idea is direct exposure of chemotherapy at doses that would be not tolerable to be given systemically, directly onto the surfaces where tumors were, and at a time when the tumor burden is lowest. So after the large tumors have been removed to treat any microscopic disease that may be on the surface or floating in the peritoneal fluid with the chemo infusion.

Dr. Freedman:

So very high intensity, high concentration right on the tumor cells in the peritoneum. And the timing, it sounds like, it is critical. How soon—are we talking days after a cytoreductive surgery?

Dr. Karakousis:

It is done actually in the same setting. So typically, the cytoreductive surgery takes place, and that can vary from just a couple hours to maybe even 9, 10, 11 hours. So these can be lengthy surgeries. After the tumors have been removed, we introduce catheters into the abdomen and infuse the chemotherapy for approximately 90 minutes under heated conditions, typically 41 to 43° centigrade. And during

that time, we are agitating the abdomen to allow for distribution of the drug and the chemotherapy throughout the abdomen. After this is completed, we remove the catheters from the abdominal cavity, we carefully inspect all of the surfaces of the viscus organs, make sure there is no untoward side effects from the therapy, and then close the abdomen properly.

Dr. Freedman:

Very interesting. And hyperthermic—so it is heated. Is that, I would guess again, for efficacy?

Dr. Karakousis:

Yes, so there is a couple of thoughts as to the benefit of the heat. For one, it is thought that the—and there is some preclinical data to suggest this—the heat seems to be more effective against disruption of cancer cells and increases the vascular permeability of the chemotherapies into the tumors themselves. There may be some direct cytotoxic effect of heat to the cancer cells, which is somewhat selective to cancer versus normal cells. And finally, it seems to allow for better penetration of the drug into the tumor. So for a variety of reasons, the heat can increase the efficacy of the chemotherapy alone under normothermic conditions.

Dr. Freedman:

Very interesting. So this heated, high concentration chemotherapeutic agent is inserted at the time of surgery for about 90 minutes and then removed and the abdomen is inspected and then you close up as you would from any other surgery. And what type of tumors are we treating with this method?

Dr. Karakousis:

Of the variety of tumors that are treated with this method, probably the most common indication are these low grade appendiceal cancers or what is clinically referred to as pseudomyxoma peritonei, and this is a situation in which patients can develop a significant amount of mucin in their abdomen, produced by the tumor cells that can be very problematic, and that may not necessarily be very responsive to conventional systemic therapies. Other tumor types that patients could be candidates for this approach include patients with limited colorectal carcinomatosis and also patients with ovarian and, less commonly, gastric cancers. Another group, which is an infrequent group but an important group to mention, is patients with primary peritoneal mesothelioma. These are patients who we more commonly hear about mesothelioma affecting the pleural surface, but it can also occur in the peritoneal lining of the abdomen and for those patients, this may be a very efficacious application.

Dr. Freedman:

Very interesting, and is this typically done in place of systemic chemotherapy in these patients, or as an adjunct?

Dr. Karakousis:

It depends on the histology. So for patients with these low grade mucinous tumors where IV chemotherapy tends to not be effective, it can be done as the primary therapy. In patients where there are more efficacious systemic therapies, like for colon cancers or ovarian, it is usually done as an adjunct.

Dr. Freedman:

So it depends on the individual tumor type in terms of what role this plays in the overall treatment of the patient.

If you are just tuning in, you are listening to “Medical Breakthroughs” from Penn Medicine on ReachMD. I am your host, Dr. Lee Freedman, and joining me today is Dr. Giorgos Karakousis, Assistant Professor of Surgery at the Hospital of the University of Pennsylvania. We are discussing hyperthermic intraperitoneal chemotherapy, or HIPEC.

Dr. Karakousis, can this type of treatment be done a second time in a patient who does not respond optimally?

Dr. Karakousis:

It can be. This is a procedure, as I mentioned, which is a lengthy procedure and a procedure that can involve hours of debulking. As a result, there can be a significant amount of scar tissue that is formed. And so, patients who are candidates for secondary HIPEC procedures have to be carefully evaluated to make sure that the indication is there. It can be done. It is a difficult procedure because you many times form a lot of adhesions from the first surgery, but it's certainly not impossible.

Dr. Freedman:

And I imagine, as you are saying, that it is a very stressful procedure for the patient. They have to have a certain functional state, or how do you assess if someone is appropriate?

Dr. Karakousis:

So, that is an excellent question. There are both tumor factors and patient factors that have to be evaluated. And to back up a minute, these are all patients we kind of evaluate in a multidisciplinary setting in the context of medical oncologists and surgical oncologists, and really, as part of a whole team to assess what is the optimal therapy for the patient.

Among the tumor factors that we look at in evaluating a patient, we talked briefly about the histology as playing an important role: low grade appendiceal cancers or other types of appendiceal cancers, the pseudomyxoma peritonei, this primary peritoneal mesothelioma. But in addition to these tumor factors, we also look at other factors, namely, that they don't have evidence of extraabdominal disease, that they are not significant viscous metastases. So a patient with a colon cancer with significant liver metastases would not be an ideal candidate likely for this type of approach. The tumor volume of disease, so patients can present with a spectrum of burden of disease from small volume disease to high volume disease, and we know that the volume of disease is a predictor in terms of the response and to this particular approach. Those are some of the tumor factors that we look at. Patient factors, as you mentioned, the functional status of the patient, their performance status, age, and just general overall sense of whether the patient will be able to tolerate a long procedure, are certainly taken into account when we evaluate these patients.

Dr. Freedman:

That is very interesting. And the thought comes to mind this sounds like a prolonged and very intense treatment, is anyone looking at this type of thing the way we do peritoneal dialysis for kidney failure patients, maybe less aggressive, but to do it on several different occasions?

Dr. Karakousis:

Yes. People have looked at giving this therapy not only at the time of surgery, but in some cases, leaving catheters at the time of surgery to instill chemo, perfuse it into the abdomen over the course of several weeks or even months after the surgery. There are certainly advantages and disadvantages to the 2 approaches. The advantage of course is of doing the, what's called, early postoperative chemotherapy, or EPIC therapy. It may shorten your time of surgery by not doing the chemo perfusion right then and there. The disadvantage is that you may not be able to achieve the benefits of the hyperthermia because you can't achieve the heated temperatures in the outpatient or postoperative setting. Also the distribution of the drug over the perfusant may not be as good when you leave the catheters because scar tissue forms fairly quickly following the surgery, and so you may have areas of loculated fluid and not get the distribution you are hoping for, as opposed to, at the time of surgery when you have really had the abdomen exposed and have sort of freed up all of the adhesions.

Dr. Freedman:

And I imagine that there have to be some side effects from this intensive type of therapy, what do patients experience as a result of this from a side effect perspective?

Dr. Karakousis:

So most of the side effects we feel from this therapy actually come just from undergoing a large surgery or a lengthy surgery. And with any lengthy surgery, after several hours of anesthesia, there are certain side effects one could expect, ranging from more surgically directly related complications like wound infections and even fistulae forming from trying to remove tumors off the surfaces of the intestine or the small bowel, to other types of complications also associated with just a long surgery like DVT or PE, etc. So the complications, I think, that tend to happen after the surgery generally are felt to result from just a lengthy surgery with a large tumor debulking. Specific complications that can happen with regards to the chemo infusate tend to be depending on what chemotherapy agent is specifically used. So, agents that are used are excreted through the kidneys, so you may see a temporary rise in the creatinine, or acute renal infection is usually uncommon and usually self-limited. There is some modest or mild systemic absorption of the drug through the perineum, although most of it stays in the abdominal cavity, and that can also lead to the kind of anticipated side effects one would expect from just a small dose of systemic chemotherapy with some mild nausea postoperatively. The chemotherapy infusate can sometimes maybe contribute to a more prolonged ileus after the surgery, and so that is something we don't...we see commonly. The patient may take a couple of more days than anticipated to have return of bowel function.

Dr. Freedman:

That makes sense that that might happen after such an intensive, concentrated dose of medication, but don't see more inflammation, postop fevers, things of that nature beyond what you would see just with a typical prolonged laparotomy?

Dr. Karakousis:

No, not typically. Again, I think the majority of the morbidity from this type of approach comes from the debulking, extensive debulking.

Dr. Freedman:

And it sounds like HIPEC is a more recent development, cutting edge type of therapy available at Penn. Is this available more widely across the country?

Dr. Karakousis:

It is. You know, the actual concept is a concept that is not as novel, this concept that is trying to instill regional or trying to do an aggressive regional approach. And a lot of people compare this to a paradigm shift in the way we view carcinomatosis or limited

peritoneal surface disease. You know, 20 or 30 years ago people viewed liver metastases from colon cancer as sort of inoperable, and now it is one of the mainstay of treatments for patients with colon metastases to the liver, is to do either surgical resection, if feasible, or a combination of ablation or embolization or other therapies. Similarly, I think the concept is for a certain subset of patients who really seem to have a peritoneal pattern spread of disease, taking an aggressive regional approach seems to make sense. And so while the concept has been around for several decades, it is really not until recently that it has been sort of more instituted. And one of the pioneers of that approach is, of course, Dr. Paul Sugarbaker, who is in Washington and has really sort of brought it to the forefront. There are increasing numbers of centers that are doing this throughout the country, but even so, it is a relatively specialized procedure that really takes the dedication of a surgical team that is familiar with these procedures, a medical oncology team that participates in the multidisciplinary decision making for a selection of patients, which is really the key to this procedure, a dedicated anesthesiology team who is familiar with these procedures and getting patients through these safely, and of course, a postoperative nursing staff that is familiar with these patients and sort of how to take care of them.

Dr. Freedman:

And do we have any data yet on efficacy compared to more standard treatments?

Dr. Karakousis:

So, the efficacy really depends on, again, the type of histology. So for patients that have this pseudomyxoma peritonei, historically those patients, with debulking alone, were known to recur with a very high incidence, and with this approach of combining the cytoreductive surgery with HIPEC, we see those recurrence rates go down. Because they are rare diseases and there have not been randomized trials for that particular histology, but compared to historical cohorts, we are seeing improvements in recurrence rates. For colon cancer, there has been a randomized trial that showed a benefit to combining the cytoreductive surgery with HIPEC, and systemic therapy compared to systemic therapy alone. It doesn't answer the question of what the relative contribution of the HIPEC is over and above the cytoreductive surgery, but it did demonstrate that the combination approach of aggressive surgery with HIPEC seemed to have a benefit compared to systemic therapy.

Dr. Freedman:

Well, I very much want to thank Dr. Giorgos Karakousis for being with us today and for describing for us HIPEC, hyperthermic intraperitoneal chemotherapy, a new and exciting therapy for patients who have cancers in the abdomen that is bringing new hope for better prognosis in these often difficult conditions. Dr. Karakousis, thank you again.

Dr. Karakousis:

Thank you very much.

Narrator:

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Duration: 16:30

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Transcriber: JP

Proofed: cm