

Advances in the Treatment of Pancreatic Cancer

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Transcript

Dr. Clancy

Welcome to **Rounding@IOWA**, a continuing medical education podcast developed by and for healthcare teams. I'm your host, Dr. Gerry Clancy, Professor of Psychiatry and Emergency Medicine and Senior Associate Dean for External Affairs here at the University of Iowa's Carver College of Medicine. Today we will discuss guidance for clinicians with their patients and family members with advances in the treatment of pancreatic cancer. Our objectives include, first, we want our participants to recognize the limitations of the traditional treatments of pancreatic cancer. Second, we want our participants to describe the new treatment pathways for cancer, including radiosensitizers. And third, we hope our participants can cite and explain the coming advances in the treatment of pancreatic cancer. Our guest expert today is Dr. Joseph Cullen. Dr. Cullen is a Professor of Gastrointestinal Surgery and Radiation Oncology here at the University of Iowa. He serves as the Vice Chair for Research in the Department of Surgery. He's a graduate of the University of Iowa Carver College of Medicine for his MD degree, followed by general surgery residency training here at the University of Iowa Hospitals and Clinics. He then completed a National Institutes of Health Research Fellowship at Mayo Clinic. He supports several graduate programs, including the Biomedical Science program in cancer biology and free radical and radiation biology. He also supports the medical scientist training program and the translational biomedicine programs. Dr. Cullen, welcome to **Rounding@IOWA**.

Dr. Cullen

Thanks for having me.

Dr. Clancy

You bet. And again, thank you for joining us and thank you for the work that you do. Joe, I just provided our listeners your official title and a summary of your training. Could you give us an idea of what a work week might look like for you?

Dr. Cullen

Usually can start on Mondays, but Mondays I operate at the VA and in the afternoons I may do some procedures at the U. Usually Tuesdays are left for meetings and research

endeavors. Wednesdays are the same. I'll do procedures if I can book them in the OR at the U. Thursdays. I have clinic at the university. And then Friday afternoons, usually every other Friday afternoon, I have clinic at the VA. Friday mornings are left for lab meetings and research meetings, basically.

Dr. Clancy

Wow, a lot of variety there and really a role model of kind of a translational researcher. You're in the lab and then you're taking care of patients in the clinic and the hospital and in the operating room as well. So a lot of multi-talents there. You're an expert in cancer and in pancreatic cancer. How did you get interested in this work?

Dr. Cullen

Basically, when I came from Mayo, my research was really on a different area. However, it wasn't that great, I guess I would say maybe. It was okay, but it wasn't really to help people in really bad diseases like pancreatic cancer. So I started collaborating with a fellow in free radical biology and medicine, Larry Oberle, who was really world renowned in the work of redox biology and specifically manganese SOD, which is mitochondrial enzyme that converts superoxide to hydrogen peroxide. And his hypothesis was that cancer cells change and they get low levels of manganese SOD as they change to be more tumorigenic. And what he showed quite nicely, and then we showed in other studies too, that if you overexpress manganese SOD, the tumors stop growing. This led to us working in pancreatic cancer. His lab was more devoted to breast cancer, but we did some similar studies and showed some differences in pancreatic cancer versus breast cancer. And we kept on working on pancreatic cancer and trying to develop treatments for it. And that led us to our last 20 years of working with high dose vitamin C.

Dr. Clancy

Excellent, excellent. So it really was the serious nature and the difficulty in treating pancreatic cancer that kind of opened the door for you of here's opportunity for patients to have a better life. So great. Well, let's start with some foundational aspects of pancreatic cancer for our discussion today. Where does pancreatic cancer sit as far as frequency compared to other cancers?

Dr. Cullen

I think it's the 4th most common cancer now in the United States. And the biggest problem is its treatment is very poor. The other problem with it is usually discovered very late in the disease where almost 80% of the patients already have metastatic disease before it's

discovered. So not only it presents very late in the disease, but it's also very resistant to any type of treatments we have.

Dr. Clancy

Do we know any risk factors for pancreatic cancer? My experience is that there's at least some random nature to it.

Dr. Cullen

Yeah, it's very random. Some of the epidemiological studies have shown that smoking is a risk factor, drinking is a risk factor, chronic pancreatitis is a risk factor, and about 10% of patients have a genetic component. In fact, since President Carter just recently died, he had two family members. If you remember Billy Carter, Billy Beer, he died of pancreatic cancer and his sister, Ruth Carter Stapleton died of pancreatic cancer. So they may have had some genetic component in their family.

Dr. Clancy

Got it. You mentioned that it presents late. When it does present, what kind of symptoms do patients have?

Dr. Cullen

The symptoms can be very vague. Sometimes they can feel full when they eat. They can have anything from diarrhea. They can have constipation. The diarrhea probably comes from pancreatic insufficiency. And one of the other symptoms is they develop jaundice. And that can be an early symptom of pancreatic cancer because it obstructs the common bile duct and causes bile to back up and then you get jaundiced.

Dr. Clancy

Sure, Well, you and I had residency in med school pretty much the same time. Over those years, what have been the traditional treatments for pancreatic cancer?

Dr. Cullen

Well, traditional treatments were anything from chemotherapies like 5FU and gemcitabine, which we use now still. And then in about 2013, there was a large trial in Europe looking at FOLFIRINOX, which is a combination of a number of chemotherapy drugs. And it showed quite nicely that you could increase their survival from about 8 months to about 12 months, 12 or 13 months. However, the problem with this treatment is it's very toxic and about 30 to 40% of patients can't tolerate it. So you have to have a very good score, I guess, basically to

even tolerate it. If you're old or have multiple comorbidities, you probably don't get it because it's very difficult chemotherapy regimen.

Dr. Clancy

So over those years, what really is the five-year survival rate with what we traditionally offer?

Dr. Cullen

Five-year survival rate, what we traditionally offer is probably up 3%.

Dr. Clancy

Wow, So I think you'd agree that modern medicine has struggled in the past with effective treatments for pancreatic cancer. In your introductory comments kind of talked a little bit about the opportunity that presented to do something better. Would you agree?

Dr. Cullen

Yeah, I mean, pancreatic cancer, kind of all the modern drugs that we use now have kind of left pancreatic cancer behind. I mean, the changes in treatments of breast cancer and lung cancer have really developed with some of these immunological drugs, but as far as pancreatic cancer, it's still the same.

Dr. Clancy

So you are a surgeon by training. Have surgical advances come along? Is there anything new on the surgical side that's been helpful for these patients?

Dr. Cullen

Well, not really. The one thing I would say from the last 40 years, if the pancreatic cancer is limited to like the head of the pancreas, you can do a Whipple operation, which is a pancreaticoduodenectomy. And treatment in that respect, The mortality of that operation, which is a huge operation, has gone down quite nicely. And that's probably the post-operative care and a lot of other things that we do now. But the operation has been unchanged for 40 plus years.

Dr. Clancy

Well, I do a lot of consultation work across the hospital. And so I'm on the surgical wards. And I certainly have seen a lot more patients with Whipple. So I can tell that the advances in the ability to do the Whipple procedure has improved.

Dr. Cullen

Yeah. the problem with the Whipple operation is, you do a Whipple operation, tumor, clean margins, tumor seems to be confined, and then eight months later, the patient pops up with metastatic disease.

Dr. Clancy

Yeah, So let's move on to your innovative work with radiosensitizers. Can you describe the field of free radicals in the treatment of cancers? How does that work? Because when I went through medical school, this was not a thing.

Dr. Cullen

[chuckle] Yeah. So radiation causes free radical, basically unpaired electrons and oxygen. And this happens during the normal metabolic processes, but we have plenty of enzymes in our cells to convert these kind of somewhat toxic species to basically water and oxygen at the end. But many drugs and of course radiation increase the levels of these reactive oxygen species. And we know cancer cells have a different kind of redox potential and you can tip them over the edge and kill them much easier with reactive oxygen species than you can with normal cells.

Dr. Clancy

Okay, good. I'm with you so far. [laughter] So next, can you explain how a combination of medications and radiation can work in the work that you do with pancreatic cancer?

Dr. Cullen

Well, in our study with high dose vitamin C, high dose vitamin C, generates hydrogen peroxide. And so we know that radiation also generates these free radicals, these reactive oxygen species. And the combination of those two can actually kill the tumor cells. And we found in most tumor cell types that when you add vitamin C with radiation, it causes synergy and kills cancers even more.

Dr. Clancy

Sure. So at a molecular level, is there more to know on this? Is there things that can translate to other cancers as well?

Dr. Cullen

Sure. So many of the reactive oxygen species damage DNA, damage lipid and proteins, and we've seen markers of all those when we use it. And so that's pretty common in most cancers.

Dr. Clancy

Sure. So is there a differential cellular impact on the pancreatic cancer cells compared to the normal cells?

Dr. Cullen

Yes. So one thing that pancreatic cancer makes it resistant to treatment is pancreatic cancer, there's a huge fibrotic component of pancreatic cancer. That fibrotic component makes it hypoxic. And so chemotherapy drugs and radiation are less effective when you have that fibrotic hypoxic component. And that's really kind of a hallmark of pancreatic cancer.

Dr. Clancy

The work that you're doing is progressing through the stages of trials. So far, how have the trials gone so far and what stage are you on as far as using high-dose vitamin C for patients with pancreatic cancer?

Dr. Cullen

Sure. So we started, we did, of course, we did preclinical work to demonstrate that pancreatic cancer cells that we have were sensitive to vitamin C. And then we did animal studies. And then we did our first phase one trial, which was published in 2013. And then we did another phase one trial where we added vitamin C to radiation. And then we just completed a phase two randomized trial looking at vitamin C with standard of care chemotherapy and stage 4 pancreatic cancer.

Dr. Clancy

Okay. Are you able to talk about the results? What did you see as far as benefits?

Dr. Cullen

Yeah, so it's been published and the trial was remarkably positive. We increased overall survival from 8 months with standard of care chemotherapy to 16 months with standard of care chemotherapy plus high dose vitamin C.

Dr. Clancy

Great. And the tolerability for the patients, you talked about the other treatments being really difficult. How about the high dose vitamin C and then the radiation as well?

Dr. Cullen

Yeah, so with the randomized trial, we saw that actually patients seem to tolerate chemotherapy better, so therefore they got more chemotherapy and for longer periods of

time. So they were able to tolerate the chemotherapy. So The question is, we know high dose vitamin C is killing cancer cells. We have a mechanism. But also I think one of the benefits that we didn't discover till recently was because vitamin C is less toxic, patients are able to get more chemotherapy and for longer periods of time. So that's a real plus. And there's other parameters that we looked at and in general, patients did better. with quality of life parameters when they got high dose vitamin C.

Dr. Clancy

And is there any side effect to the patient from the high dose vitamin C itself?

Dr. Cullen

The biggest side effect is patients get thirsty when they have the infusions because it's a high hyperosmolar salt load and so patients will get thirsty. Some will get hungry actually too, and that's not a bad thing. Once the infusion stops, those usually go away. There's a risk of developing kidney stones. However, actually we've only had in over 200 patients, we've only had like one or two that actually developed kidney stones. So the chance of that is fairly rare.

Dr. Clancy

I imagine when you're describing this treatment to the patients because it's vitamin C and it's been around for a long time, they're maybe a little bit more open to it. Have you seen that?

Dr. Cullen

Yeah, But on the downside, they think that if they ingest a ton of vitamin C that you buy at Walgreens, that'll work the same and it won't. You won't achieve the same levels unless you give it IV.

Dr. Clancy

Yeah. And have you seen patients coming to you and have already done that with vitamin C? They've done their own research and they're already taking their own oral amounts of vitamin C.

Dr. Cullen

Yes, yeah, it happens all the time. I get two to three emails a week from people from the outside internationally asking me, if I take 1000 milligrams of vitamin C orally today, will that do it too? And then no, it won't.

Dr. Clancy

Yeah, I try to explain that all the time to patients of every drug has a differential effect at dose and has a differential effect on how you give it as well between oral and inhaled and IV. Totally different, totally different. I mean, we see that with ketamine. Ketamine is a quite variable drug depending on the dose and how you give it as well. So in your protocols, what's next? What are you planning for now that you've been successful with the phase two?

Dr. Cullen

Well, our colleagues, our collaborators here at Iowa have published a phase two that was not randomized in glioblastoma and they showed very positive results. and we're just winding up a trial in lung cancer with vitamin C and radiation and we have one more patient to be entered. So we'll look at the results of that when that's done too. As far as pancreatic cancer, we'd love to do a multi-institutional randomized phase three trial and we're looking into the possibilities of that, but it's going to be very difficult without big pharma support.

Dr. Clancy

I was part of the phase three trial for the Pfizer covid vaccine. And a big step up from phase two to phase three. So as you plan this next phase, how much bigger will the study be?

Dr. Cullen

Well, in our study that we just published, I think we had 36 patients. And depending on how soon you want the results, it probably looks like about 96 patients we'll need in various sites to enroll.

Dr. Clancy

And you've done this for a while. What's your timing look like? How far off do you think the next phases of research may be? Are we looking maybe phase three in the next year or two and maybe phase four, another three or four years out?

Dr. Cullen

Yeah, I think in a best case scenario, that would be it. Yeah. But like I said, we just, as you know, for phase three trials, the amount of money needed to do this is just something we don't have right now.

Dr. Clancy

Yeah, So as we look to the future, what advances do you see on the horizon for using combinations of medication that radiosensitize with radiation for pancreatic cancer, but for

other cancers as well? Is this an expanding new Ave. for treatment of lots of different cancers?

Dr. Cullen

I think it is. You know, I know a couple of researchers here and at the University of Nebraska are using some type of radio protectants too. The problem with radio sensitizers is it can also harm normal tissue. So you have to be careful with that. There's only one approved radio protectant and radio sensitizer that I know of on the market. And I think the results are kind of not that great. The other area of interest is superoxide dismutase (SOD) mimetics, which have some promise as far as radio protectants, which I think could be extremely useful in pelvic type of radiations, either prostate cancer, cervical cancer, or even rectal cancer.

Dr. Clancy

Yeah, you're taking on some of the really tough ones, pancreatic cancer, glioblastomas, cervical cancers. It's really heartening to see that there's new opportunity out there that what used to be pretty daunting expected outcomes, there's new opportunity. So really great work. Thanks for the great review of where we are. What are some of the take home points you'd like to leave with our listeners on where we are with pancreatic treatment and where we may be?

Dr. Cullen

Well, we kind of touched upon this, but if you give oral vitamin C, you get micromolar levels in the blood. And at micromolar levels, the vitamin C acts as an antioxidant. However, what we do is give massive doses instead of 500 milligrams orally, we give 75 grams IV. And at IV, it bypasses all the mechanisms involved in the body to lower vitamin C levels and we overwhelm those. And so we get millimolar levels in the blood and that kills the cancer cells. So that's really the huge take home message from this. But one thing that we didn't touch on is What we've shown with radiation, that vitamin C radiosensitizes the tumor and acts synergistically with radiation. But what we found in our other studies is it actually protects normal tissue. And we've shown that actually in human tissue, that the vitamin C given IV actually protects the normal tissue during radiation, which I think is another plus on it.

Dr. Clancy

So it really sounds like. We have several win-wins here that it's pretty easily tolerated. It's protective of tissue that we want to protect. It sensitizes the tumors and it allows the ability

for patients to have additional chemotherapy over a longer period of time. So that sounds like a win-win-win.

Dr. Cullen

I think so, yes.

Dr. Clancy

Yeah, it's really good. As we finish up, anything else you'd like to add?

Dr. Cullen

No, I mean, part of the The great thing about the University of Iowa is this is such a collaborative effort. I'm kind of the person out there talking, but I have colleagues that even from day one when I started here 32 years ago, the colleagues here are just fantastic as far as collaboration. And the collaborations I've struck up with people have just been great. And this is not only collaborations in basic science, but medical oncologists were very reluctant to do this here at Iowa. And Dan Berger was one of the medical oncologists that tried it for the first time and they've seen the results in various tumors and they're excited. And then we have phenomenal research nurses who enroll these patients and are just fantastic.

Dr. Clancy

Yeah, it's a big part of being the National Cancer Institute designation that we have. They expect the collaborations across the lines and we actually are able to walk the walk here.

Dr. Cullen

I agree. Yeah, it is great.

Dr. Clancy

Well, to our expert, Dr. Joseph Cullen, thank you for joining us on **Rounding@IOWA** and for the work you've done helping patients and families really ease their suffering and add years of life. It's wonderful work that you do. And to your collaborators as well, thank you. For our listeners, you can access instructions for CME and CEUs within our show notes. And as always, we hope you'll join us again for another session of **Rounding@IOWA**.

[Upbeat theme music plays]