

Upper Tract Urothelial Carcinomas (UTUCs)

Part III: Clinical Trials and Emerging Therapies for UTUC

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Dr. Matin: So this is actually a very exciting time for us who treat this disease because up until two years ago there really was nothing happening. But starting in 2015 we had our first ever national cooperative group trial open and this, actually, is a non randomized study looking at the benefit of chemotherapy before removal of the kidney and ureter. This study is designed to look at patients who have both good, as well as not so good, kidney function, so it's two arms based on the status of the kidney function. What's very gratifying is that despite initial concerns that maybe we could not enroll enough patients from this uncommon disease, we actually were able to fully enroll in one of the arms within a couple of years. The second arm, which was for patients with more compromised kidney function, is still open to enrollment, but I do anticipate that to also complete maybe in the next year, and hopefully we should have a read out on the results of this within a year or two and this should help confirm what we have seen on prior retrospective studies.

Now this particular protocol or clinical trial is for patients who have high risk disease, and so patients who we worry that surgery may not be enough to bring a good chance of cure. So these are patients with high grade tumors, and the advantage particularly of giving the chemotherapy first is because that is when patients have the best renal function. Once we remove the kidney and the ureter, the kidney function dramatically decreases.

We have several studies that show that up to 80% of patients who have surgery are really unable to receive effective chemotherapy after surgery. So really the best time to do it, we think, is before surgery is done, when the best kidney function is present.

Until 2015, there were *no clinical trials* in USA for UTUC...

- 2015 First ever national cooperative group trial
 - ▣ Tested the benefit of chemotherapy before nephroureterectomy
 - ▣ 2 arm study based on kidney function
 - ▣ May 2017 Arm A fully enrolled (30 patients)
 - ▣ Arm B continues enrollment

So within a year after that, another very exciting thing happened which is that a company developing a new drug was interested in treating the disease. This is actually quite a milestone also, because up until this time such a thing had never happened. What's interesting about this is that it's not really a drug but a drug device combination. The drug is mitomycin-c, a chemotherapy, actually was initially developed as an antibiotic, initially discovered in 1963. It turned out to be fairly toxic as an antibiotic, but was pretty effective because of toxicity to treat cancers. We have actually used this for urothelial cancers and dripping it in the bladder or, in some cases, the upper tract, to try to prevent recurrence of disease.

2016 First drug trial for UTUC

- Actually, a drug-device combination:
- Drug: **mitomycin-c (MMC)**....used for decades (discovered in 1963)
- Device: a new **reverse polymer hydrogel**
 - Liquid at cold temperature
 - Gels at body temperature
 - Dissolves slowly in liquid (urine)
- **"MITOGEL" = MMC+hydrogel**

* At room temperature

The device is really what's unique. It's not so much a device as you might think like a tool, but it's really a gel. This gel has a unique property in that it does the opposite of what you might think most gels do, like jello, because it's liquid when it's cold and then it becomes thicker when it comes up to body temperature, and then subsequently it dissolves slowly in liquid, such as urine. So this product, the combination of the mitomycin with the hydrogel is called mitogel. What this graph shows you is basically the fact that when it's cold it has the consistency of about motor oil, but then as the temperature goes up

it quickly becomes more viscous and thick and turns into this gel that can sit in a cavity and then slowly be dissolved.

So the idea here is that somebody can received the mitogel as an outpatient within the renal pelvis and the ureter, and what this would allow to happen is that higher doses of the chemotherapy, and longer exposure of that internal urinary system to the chemotherapy, possibly improving it's ability to eradicate and, as well, prevent urothelial cancers. So it treats the internal urinary system from all the way in that renal pelvis, down the ureter, and even the bladder, and then the patient of course urinates to get rid of this as urine is being produced. We don't think it's going to be absorbed by the body. It's topical therapy, basically. It's as if putting cream on your skin, except if you think about it as an inside out skin.

So this neat little video kind of gives you a visual of what happens where, again as an outpatient, the patient has a cystoscopy done. We pass that tube up into the ureter and into the renal pelvis, and then under xrays we can visualize the gel going in. This just ... I think the video's restarting, which is fine, but basically showing some of the things that we've talked about, about removal of the kidney and the ureter being a standard. This is what the gel looks like. It's liquid when it's cold, with all the ice cubes around it and then, as was shown previously, we inject it up into the renal pelvis. As we do so it basically goes into all the little crevices within the renal pelvis. It gels, and then as urine is being produced it helps dissolve the gel, as well as the chemotherapy, and basically allows it to contact the tumors and slowly eradicate them. This happens over the course of four to six hours depending on how much you give. As mentioned, this is currently ... is something that we're using under a clinical trial.

And so, as opposed to that initial trial that I showed you which was for high grade tumors and high risk tumors, this is really for low risk tumors. Now this doesn't mean that they're of any lower priority for us. It does mean that they're low likelihood to metastasize, but they are a major burden for the patient. They tend to recur. They're difficult to treat for reasons that were previously explained by the other speakers, and so currently, for this clinical trial, this is indicated for low grade small tumors up to 1.5cm. You could have multiple tumors being present, it's just none of them can be larger than 1.5 cm. It is open label, meaning you would know what you're getting, and it's single arm, meaning that patients who enroll for sure will get the drug if they are eligible.

Then this little schematic shows what happens. In the first one to three weeks we perform screening to make sure that it's safe for the patient and they're eligible. Then the treatment is given once a week for six weeks, similar to what we do for treating bladder cancer with topical therapy. We then give three weeks of rest, and then we evaluate the patient with repeat ureteroscopy to see if there has been complete eradication of the tumors or not. If there has been that's considered successful and the patient can actually get monthly maintenance therapies. If not, then if they don't receive maintenance, then we just continue doing follow up.



Now this is a trial which is being monitored by the FDA and was approved by the FDA so really it would be, again, another major milestone for this disease, first of all because it would be the first drug ever approved for this particular disease, but secondly, because it has the potential to completely change how we treat low grade upper tract urothelial cancer. You know, currently we have to do multiple endoscopies. We often have to take out kidneys and ureters because of the recurrent pattern of these tumors, and so we do hope that it will be an improvement over our current therapies. What's exciting is that this study, while it is enrolling really well nationally and internationally, it is probably going to be open still for another six or nine months. We anticipate about that period of time based on the current rate of enrollment, and a lot of the speakers that are actually on this panel are also directly involved at their centers, for anybody who may be interested out there who's listening.

Now there are some other treatments and promising paradigms on the horizon. There is a stent being developed with a similar idea, where chemotherapy could be loaded into it, the stent is then placed, and then the chemotherapy slowly dissolves out treating the urinary tract over a longer period of time than we can currently do. This is still in the very early prototype stages, however.

The other thing that's very exciting that's happening in patients who have incurable disease there's this new generation of immunotherapy drugs that are called generally checkpoint blockade. This is really changing the whole landscape of how incurable urothelial cancer is being treated. What's interesting about upper tract cancer also is that there's a high rate of mutations and unstable genes and this, we think, is a factor that may make them more susceptible to immunotherapy. So while these new immunotherapies are not approved for

Other treatments are on the horizon

- New Generation Immunotherapy (checkpoint blockade)
 - ▣ Currently approved only for incurable urothelial cancer but potential in future for use in localized UTUC
 - ▣ High number of mutations and unstable genes in UTUC make it more susceptible to immunotherapy

treating patients with, for example, low grade disease, or localized disease, there is this idea that over time these treatments will trickle down to these lower stages, as long as they could be well tolerated in this patient population.

Dr. Steinberg: Also, you know, one of the things about those tumors that have many mutations, especially in the Lynch Syndrome and micro

satellite instability and so forth, they're looking at a whole new generation of drugs called the parp inhibitors. Can you come in a little bit on that while I have you on the phone?

Dr. Matin: I can speak only a little bit about it. I'm also still, you know, familiarizing myself with that. But some of the genetic studies that we have done on upper tract cancer, which also goes along with what we see in bladder cancer to some degree, is that there are these situations of patients who have no tobacco exposure, no industrial exposure, a lot of women, actually, who are never smokers. What we notice when we do their genetic analyses is that some of the mutations are related to DNA repair genes, basically a malfunction in the ability of the body to repair problems in their DNA, something that otherwise every cell in our body should be able to do. So the idea with the parp inhibitors is that it could help reverse that to some degree. So I do think that's probably some time away, Gary, but maybe you can comment a little bit in terms of what could be coming out?

Dr. Steinberg: Absolutely, and I think that we're seeing parp inhibitors in a variety of tumors, especially the ones where we see a high mutational load and these ... in the colon cancer realm with the micro-satellite instability, as well as in the ovarian cancers, breast cancers. So I think it's a whole new avenue of treatment. Again, I think it's related to the fact that we've done the genomic analyses in muscle invasive bladder cancer, mainly through the Cancer Genome Atlas Project, but also a lot of individual investigators, such as at your institution at MD Anderson, and so forth, and Baylor, and Sloan Kettering and Hopkins, and so forth, that have done these studies that are helping patients, helping us to personalize their therapy to make major inroads in curing a lot of patients with these devastating diseases.

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