Update on Precision Medicine & Bladder Cancer

Part I: What is Targeted Therapy?

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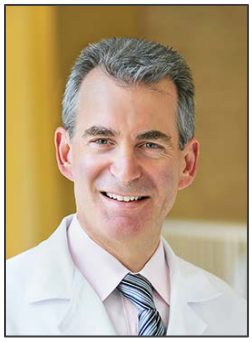
BCAN Patient WEBINAR SERIES

Presented by:



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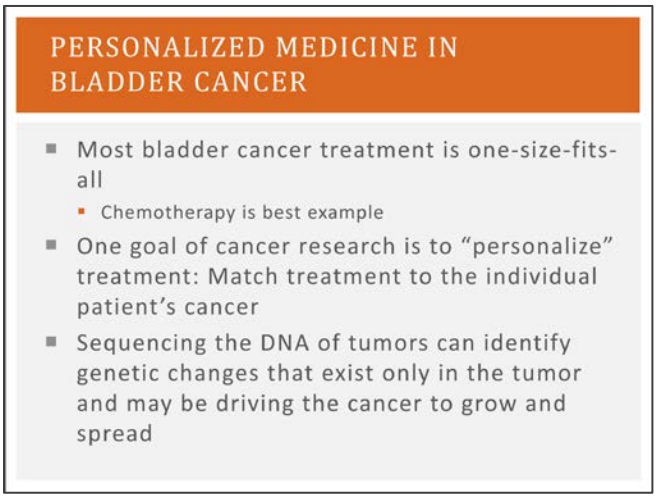
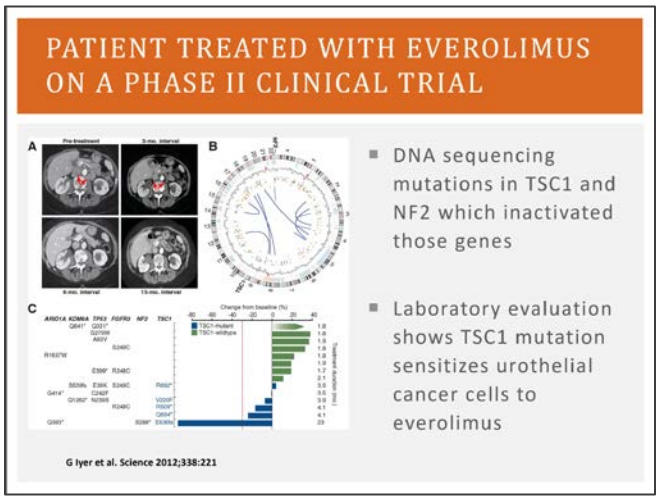
Dr. Lerner: I'll do a bit of an introduction and talk to you a bit more specifically about The Cancer Genome Atlas Project. Today, unfortunately still, most bladder cancer treatment is one size fits all, and chemotherapy is the best example. We have effective chemotherapy drugs, but we don't quite yet know how to identify the patients that are most likely to benefit from the chemotherapy. Obviously, those are the ones that we want to treat, and by the same token, identify patients who are not likely to benefit from chemotherapy, and that we might try some other approaches that you'll hear about tonight. One goal of cancer research is to personalize treatment, in fact match the treatment to the individual patient's cancer, best treatment for the appropriate patient. As you'll hear, sequencing the DNA of the tumors can identify genetic changes that exist in that specific tumor in that particular patient that may be driving the cancer to grow and potentially spread to other parts of the body.

It's exciting because there are many new cancer drugs that are approved for use in other types of cancer, and oftentimes targeting some of these alterations in the DNA of that particular cancer. They're in early stages of testing in bladder cancer as we're now learning about some of the genetic changes that are in common with some of these other tumor types. A particular drug may be expected to work in a patient with that specific genetic change but not in a patient without that genetic change. We'll go into this in a bit more detail in just a minute.



This is really a fantastic example, and a paper that was published by Dr. Iyer a few years ago. This was a clinical trial of a drug called everolimus that was led by Matt Milowsky when he was at Memorial Sloan Kettering. It was a Phase II trial. They had had some indication of safety and some early signals of efficacy. Everolimus targets the mTOR pathway, which is altered in a small but significant percentage of patients with bladder cancer.



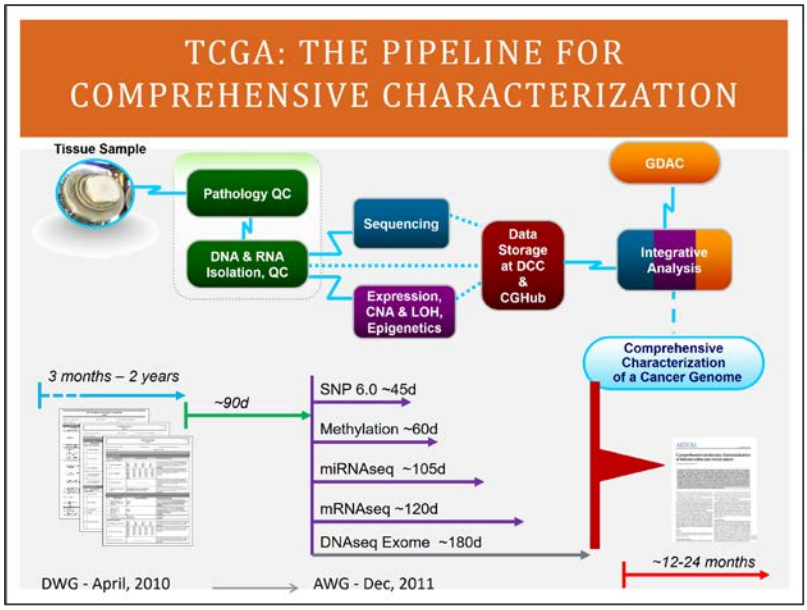
I don't know if you can see up here in this CT scan, but this patient had a lot of lymph node metastases in what we call the retroperitoneum, outside the bladder. As she got treated, you can now see that even 15 months later, there's no evidence of this. What Dr. Iyer and his team went back, and they took this particular patient and sequenced the tumor, and lo and behold, found alterations in this mTOR pathway or TSC1. Everolimus targeting that accounted for what we call an exceptional response. Even though the overall trial was negative for everolimus in general, in this particular patient, it happened to be lifesaving. This is the promise, and our duty as physicians and scientists is to figure out how this can be applied to more patients, and not just with drugs that target this particular pathway.

Coming back to cisplatin-based chemotherapy, which is our go-to chemotherapy, and more recently immunotherapy, it becomes standards of care for patients with advanced bladder cancer. As I've already mentioned, there have been now a number of reports just like the one I showed you, some also targeting mTOR but some targeting other pathways, that are beginning to shed light on the biology and the potential therapeutic targets for drug development.

You must be living under a rock, so to speak, if you haven't heard about the explosion in immunotherapy. We're fortunate that since May of 2016, there have been five of these new exciting drugs approved for advanced bladder cancer. As exciting as the data are and the results are, probably only about a quarter of the patients ultimately will benefit from this new form of therapy, leaving a large percentage of patients still in need of innovation. This is what we're going to be talking about during this webinar.

I'd like to share a little bit of information about The Cancer Genome Atlas Project. This was a very innovative idea designed by or funded by the National Cancer Institute, starting about eight to 10 years

ago. Think about it as a Human Genome Project for now 26 common cancers and seven rare cancers. We were fortunate that bladder cancer was selected for this project, muscle-invasive bladder cancer.



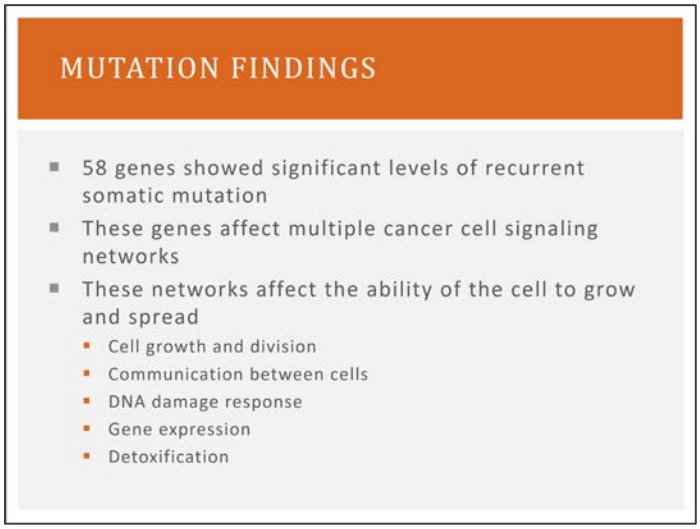
Basically, the idea is that tumors were actually submitted from 33 different sites that were participating in the bladder cancer project. In this project, you get the DNA, the RNA, the protein. You get all of the potential alterations in a patient's tumor that could potentially affect the biology, the growth, how it responds to different treatments, and then you have this integrated analysis that results in what is commonly referred to as a marker paper. We published the first results in 2014, and what I'll share with you now is the results now on nearly tripling the number of tumors to 412. Think about it as a comprehensive characterization of the cancer genome, in this case of muscle-invasive bladder cancer.

We confined it to muscle-invasive bladder cancer because that's clearly the most significant form of bladder cancer that affects roughly about a third of patients diagnosed with bladder cancer and is the most lethal form of it. That's where we decided we could potentially have the biggest impact. That's going one too fast. None of the patients could have had prior chemotherapy or radiation, because that clearly alters the DNA. We wouldn't really necessarily be able to identify changes in the DNA or RNA that were unique to the tumor as opposed to being caused by chemotherapy or radiation. The DNA alterations are identified by sequencing all of the gene sequences that are then turned into proteins. That's really where you can really learn about the genetic machinery of a particular tumor.

Some of the things that we found are that bladder cancer has a very high mutation rate. Mutations are alterations in genes that ultimately lead to altered proteins that are not functioning in the normal way that a protein should be functioning, and how that affects growth of the cell, and multiplication and division of the cell. This is very similar to other cancers that have high mutation rates, lung cancer and melanoma, that are also felt to be carcinogen-induced cancers. You may be aware that about half of patients with bladder cancer have a smoking history, and we know that cigarette smoking is a major cause of bladder cancer.

Some of the other urinary tract cancers, for example kidney cancer also known as renal cell carcinoma, or prostate cancer, have much lower mutation rates, distinguishing them from bladder cancer. One of the things is, despite the common history of cigarette smoking, it didn't seem to affect the mutational frequency or the type of mutation. That potentially could be an artifact of the study, since the

overwhelming majority of patients in the study had bladder cancer, but it's an ongoing area of research to try to understand why this relationship at least in terms of mutational frequency didn't show up.



One of the really exciting things is that we identified 58 genes that had a significant level of recurrent mutations. This is important because among these 58 genes, 34 of them had not been described before as significantly mutated genes at any frequency in bladder cancer. One of the benefits of having more tumors in the cohort was that we could identify some of the less common genomic abnormalities, and if you happen to be that patient with that particular gene alteration, and there's a drug that could target that, that could potentially be lifesaving. That's the research that we have to do moving forward.

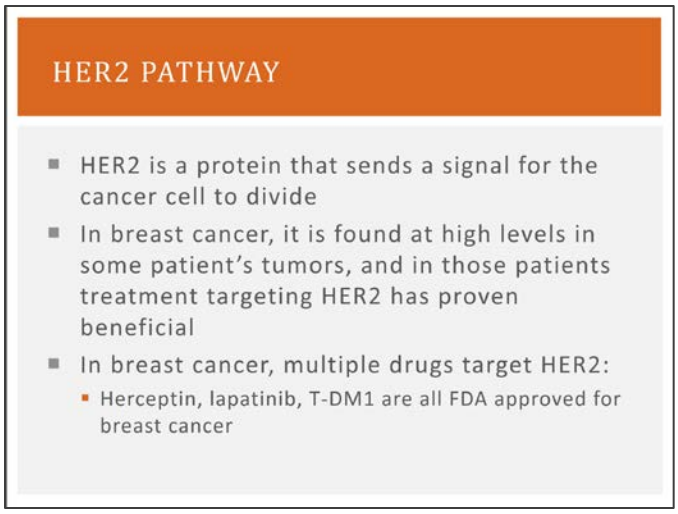
When you have all of the information about the DNA alterations, and RNA, and protein, you can put this together in what some people refer to as a network analysis or pathway analysis to look at all of these different alterations that can affect how cells grow, what makes a cancer grow, what makes a cancer spread, and what makes a cancer respond to a particular type of treatment.

We're going to talk a little bit about some of the signaling pathways. A signaling pathway is how cells normally communicate with one another to function as part of an organism. It's the same for insects all the way to humans. These pathways send signals for cells to divide and grow. The problem with cancer, it's very simple. It's altered or uncontrolled cell division or growth. The pathway would normally switch off, like a light being turned off, but in cancer that light is stuck in the on position when it really should be in the off position. There's a whole number of ways that this can happen, and the Genome Atlas Project really has contributed significantly to our understanding of how these things occur.

Let's talk a little bit about some of the specific alterations and get a better understanding of why cancer cells don't obey the usual stop signs that tell the cancer not to grow. This is one of the exciting things about one of these new immunotherapy drugs, that are basically blocking the signals to the immune system that are preventing the immune system from recognizing the cancer as abnormal. The more we understand about these pathways, and now including the immunotherapy, we can really begin to understand how to change this paradigm of the accelerator being stuck in the on position and uncontrolled cell growth.

Let's talk about the HER2 pathway. You may have heard about this in breast cancer. HER2 is a protein that sends a signal for the cancer to divide. In breast cancer, it's found to be at high levels in some patients' tumors, and in those patients, there's excellent data showing that if you target that HER2

alteration, those patients have a significant benefit in terms of the cancer, a complete response to chemotherapy drugs targeting HER2. There's multiple drugs that target HER2. I've listed some of them here. They're all FDA-approved for breast cancer.



We can try these drugs in patients with bladder cancer that have HER2 alterations. That's as many as 15 to 20% of tumors in The Cancer Genome Atlas Project. I have here 7% and 5%, but actually what we found was, if you look at all the ways that HER2 is altered, it's closer to 15 to 20%, very similar to the frequency in breast cancer. We're excited, because there's clinical trials going on that target HER2 with caution. Some of the early trials have not necessarily shown a benefit, but research continues in this area to try, because we have these FDA-approved drugs that we can now apply in the setting of bladder cancer.

Another common alteration is FGFR3 mutations. This is the fibroblast growth factor receptor 3. We know that it's important in the more ... not benign, but the type of bladder cancer that's much more common, non-muscle-invasive bladder cancer, low-grade bladder cancers that really are much easier to treat by removing the tumor and the bladder. Sometimes we'll give chemotherapy in the bladder, but they really have a much lower risk of spreading beyond the bladder. While these FGFR3 mutations are identified in about 70% of those cancers, they're also present in about 15 to 25% of cancers that are muscle-invasive, and they're also present in a smaller percentage of patients with metastases. We're fortunate that there's multiple drugs that target FGFR3. They're being tested in virtually every stage of bladder cancer, and this is perhaps the quintessential paradigm for targeted therapy that's being tested in bladder cancer in all stages.