cancer NEWSLINE

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>> Welcome to Cancer Newsline; your source for news on cancer research, diagnosis, treatment, and prevention. I'm your host Dr. Oliver Bogler. Our guest is Dr. John Mendelsohn, professor in genomic medicine and past president of MD Anderson, and our topic today is personalized cancer therapy. Dr. Mendelsohn, the genomic revolution in biology and medicine has made treatment tailored to a person's disease possible; so-called personalized or precision medicine. How does that work and why is it better than conventional treatments?

>> Well, it's a very good question and the answer would take a while. Let's say 12-15 years ago, the diagnosis of cancer was made by looking at a piece of the tumor on a microscope slide and the pathologists were able to differentiate whether it was malignant or normal breast or malignant or normal colon, and then whether it looked like it was more malignant, more severe, or less severe basically by the amount of abnormality in the cells under the microscope. And this served us pretty well, but left much unknown and then about 15, I guess it's almost 20 years ago now, we were very sure that cancer was a disease caused by aberrations in genes; mutations or rearrangements or damage to genes. Genes, of course, are the code that produce all the proteins and all the components our body is made of. So, if the gene is damaged, your body is damaged. Well, once we knew that abnormalities in genes can cause cancer, the question is can we take each individual patient and see what genes are abnormal in that patient? And it turns out that for, let's say colon cancers, the abnormal genes in one patient with colon cancer are not the same as the abnormal genes in another, although some of them do overlap. Now, if we'd try to do that in 1995, it would've cost around two to three billion dollars and it would've taken a few years to sequence the genes in one patient's tumor. When we do that today, it takes about three days, it costs under $5,000, and the answer can come back into the physician within a week or so. So, we've made incredible progress in being able to interrogate the individual tumor and see which genes are abnormal in each patient.

>> And then how can that knowledge be used to, to improve cancer treatment?

>> Well, of course, that's the next important question. It didn't go unnoticed among researchers in pharmaceutical companies and biotech companies and universities that aberrant genes are the cause of cancer. So, the next logical step is why not make drugs that attack the products of those genes? If the products of those genes are causing the cancer and if we can disarm those products, with a drug or an antibody, we might be able to treat the cancer. And, for me, this is very exciting because I began my own research in 1980 with the hypothesis that we might be able to disarm the product of a gene called the EGF receptor gene and when we proposed this, to tell you the truth, it was thought pretty far out. We wrote a grant proposal and it was turned down, but we persisted. And my colleagues and I were able to make an antibody that bound to a receptor on the cell's surface called the EGF receptor, and blocked EGF from binding to the EGF receptor. Now, what does that mean? Well, if you put your key in

the ignition in a car and turn it, there's an electric signal sent a whole lot happens in a car and if you pull the key out, the signal is gone. And in cells, it's a chemical signal, not an electric signal, but there are a lot of key holes on the surface of cells and a lot of keys that can go to the cell, stick into the key hole, in this case, binding to the receptor on the surface of the cell, and send a chemical signal that tells the cell to proliferate or do other things. So, this approach to hundreds of genes now, has been taken, both in academic institutions and in commercial entities, and today I estimate there are over 800 molecules. Some of them are small molecules that you can take orally, some are antibodies, which you have to give intravenously, that can be given to patients with specific gene aberrations that have a high chance, not a guaranteed chance, but a high chance of affecting the health of the tumor cell that bears that gene aberration.

>> One way that we can find out whether a tumor is a good candidate for a particular precision therapy is through a biomarker and you and your colleagues recently did a survey of over 300 phase one trials with over 13,000 patients. What did you learn about the importance of biomarkers?

>> Well, so the biomarker, in this case, might be the EGF receptor. If it's present on the cell, and it's present on many kinds of cancers, then that cell might be targetable with the product we produce, which binds to the EGF receptor. But in this case, we were working very early with a particular gene aberration. Now, we can study and ask for a list of gene aberrations in each tumor and there may be dozens, there may be hundreds in some lung cancers and melanomas, there are even a thousand gene aberrations. The new drugs that have been developed to treat cancer, target these, the products of these aberrant genes. Now, what do you do when a new drug comes out from a drug company and you need to test it in people? It goes through three phases and the first phase is just looking to see if it's safe and trying to figure out the best dose to give. And in the past, when a new drug came out, we took patients with advanced cancer, any kind of cancer, and gave them this experimental drug, this required, informed, consented patient. It required approval of the FDA. It's very carefully regulated for patient safety, which is very appropriate, and we did these experiments for, MD Anderson is a leader in doing this. We do this on a thousand different tests every year. The test being testing in patients a new drug. Well, now we have a new wrinkle. We know what the target of the drug is. So, many researchers, clinical researchers, ask the question well, if you give A, can we prove that if you give an experimental therapy to patients that have the aberration in the target of that experimental drug, will they do better than if you give the experimental drug to any patient with advanced cancer? Which is what would have happened before this sequencing technology became available. And, my colleague was Razelle Kurzrock, did a meta-analysis. That means she went over all publications of studies of new drugs that were approved by the National Cancer Institute and studied in protocols that were approved by the National Cancer Institute. And asked this question and indeed, she found that if the experimental drug was matched to a patient, in the way I just described, the patient had a much better chance of responding to that drug than if the drug was given to any patient with advanced cancer. That's very reassuring because that says we're on the right track.

>> That's a tremendous advance. So, what advice would you give on that basis to patients with cancer who are seeking a clinical trial?

>> Well, the advice we give our patients today is there are a lot of excellent standard of care therapies available today and when I was born, only a third of cancer patients live five years or more and today, two-thirds live five years or more and the majority of those are actually cured, although we can't

guarantee each individual patient is cured. If you have been given a standard of care therapy and it's worked, you don't need to worry about the genes. Go enjoy life, but unfortunately, I said two-thirds, so one-third of patients die of their cancer within five years. Those are patients where standard therapy has failed to achieve the goal we want and those are ideal candidates to have their tumor genes sequenced and to volunteer to have experiments performed in which they receive drugs that are not yet approved by the FDA for general use, but are approved for research, try these drugs out, picking drugs that target the abnormalities in their tumor. And about half the time now, we're able to sequence the tumor and find an experimental drug either here, or at some other cancer center, that our patients can sign up for and try out.

>> Dr. Mendelsohn, thank you very much for speaking to our listeners today.

>> You're very welcome and you can tell I'm very enthusiastic about this, this change in cancer medicine that has occurred, that's why it's called personalized.

>> For more information, visit mdanderson.org. Thank you for listening to Cancer News Line. Tune in for the next episode in our series.

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