

Beyond Traditional Treatments for Lung Cancer: The Roles of Molecular Medicine and Individualized Therapies (Video Transcript)

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Featuring:

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Originally the title for this talk Dr. Salgia recommended was, “Targeted Therapy,” and I called him up and I explained to him that I wasn’t happy with that title. I changed it to the one here that I won’t read for you, and I think he was a bit puzzled as to why I did this and our chief of oncology, who also is a lung cancer specialist, Dr. Vokes, explained that Maitland is the kind of doctor where when two words would do, ten could be even better.

The real concept for this presentation today, and you’ll see in a few minutes why I changed that title, relates to understanding – in the history of development of cancer drugs, where have we come from, where are we going and what can we do today specifically to improve treatment of lung cancer, and so these are the themes of the talk for the day.

I open up with this short story from the October 9th *New York Times* with a very exciting announcement that cancer can be cured and that this famous Dr. Doyan gave a presentation in Paris explaining some new surgical techniques and this is very exciting until you realize that this was initially published in *The New York Times* in 1909. This is why I pause for a moment before using a buzzword. Buzzwords are helpful because I think they get complex concepts across to people. They’re easy to use and communicate, but as you’ll see, they’ve gotten us into trouble with, I think, raising expectations too high for patients for the American public and lead us to a situation where the progress that we’ve made sometimes is under appreciated because of the disappointment in relationship to the original hype. To understand this, the history dates back to this gentleman, Paul Ehrlich, who won the Nobel Prize in 1908 for his work in immunology. He was a chemist who is thought of as the Father of Chemotherapy because he was the first person to appreciate the idea that you could develop a compound that could specifically affect certain cells in the body without harming the rest of the body and based on an opera that was popular in Germany at the time, he referred to this time as using magic bullets.

We have to fast forward ahead about 40 years to a time when these two gentlemen were very actively involved in the development of the first cancer drug. It has a long name, when you talk to a chemist like Dr. Gilman featured here on the left, but we can refer to it as mechlorethamine or

nitrogen mustard. The concept for nitrogen mustards evolved from studies exposed to nerve gas from World War I and the recognition that one of the damaging effects of these agents was on the production of white blood cells by the bone marrow.

Dr. Farber, who is a pathologist and pediatrician, recognized that childhood leukemias were an overgrowth of white blood cells and is there some way that we could manipulate a compound that damages the bone marrow and then use it in a proper dose in order to treat childhood leukemia and indeed, that is what Dr. Farber accomplished with compounds that were developed by Dr. Gilman and hence you had the first chemotherapy.

Over the ensuing 10-15 years this generated much excitement. Many compounds were first developed and shown to first be effective in different cancers. This became a very popular issue for the American public and the federal government got involved and actually began the National Cancer Institute and so you see here in 1959, excitement on the new war on cancer combining both virus research and development of chemotherapy.

Then we fast forward again now another 20 years and we had yet another cover of *Time* magazine, but this time chemotherapy had not lived up to all of its hope and instead immunology was the hot idea and biotechnology. One of the biotech companies succeeded in purifying this compound, interferon, a protein that would interfere with growth of viruses and growth of tumor cells as being the next drug that might cause a revolution in cancer. As you well know, this is not something that is routinely used these days. Many other items and agents have been suggested as being the next cure for cancer and finally, the editors of *Time* wised up a little bit and decided that they would do a cover story on an issue of how to tell hype from hope. This is what we want to do to cancer, but how do we control the message, how do we communicate with patients and the public to understand what we can accomplish and in what time frame we can accomplish that. And so despite the article just three years before hand, the editors of *Time* then decided to promote our latest round of agents, the first drug that we would consider to be targeted therapy in the modern sense of the term is Gleevec and you see this rather laudatory title of this cover page and one would say that Tarceva and other drugs that many of the patients even here in this room know is effective and helpful for lung cancer patients, but is not a cure, also fits into this category of sort of the new magic bullets.

However, some had begun to criticize the whole process and, in fact, the cover story in *Fortune* in 2004 questioned whether we've been doing this the right way all along and so what I hope to tell you today is show you some evidence that between the type of work that Dr. Salgia just described for you, primarily in the laboratory, and some of the more advanced clinical research that we've been doing across the country as well as here at the University of Chicago, might be a more rational and promising, but cautious approach. You see that Dr. Klausner, who was the head of the National Cancer Institute at the time said, "The history of cancer research has been the history of curing cancer in the mouse. We have cured mice of cancer for decades and it simply didn't work in people." And I hear some hissing in the crowd and I appreciate that. I think that this has been a fundamental flaw, but I think that now is the time for some cautious optimism, as well as activism.

As Dr. Salgia described for you, we have three new drugs approved in the last three years for lung cancer. I mean, that's amazing! And there are more that are in development. We have exciting prospects for screening to find disease early, just reported a few weeks ago. Of course, we have ongoing efforts to make current, curative treatment such as radiation and surgery more precise,

more effective and available to more patients, and we have learned that using adjuvant help chemotherapy in lung cancer as we've been using for years in breast cancer and colon cancer actually increases the number of people who get cured of this disease.

As Dr. Salgia showed you earlier, one issue in terms of trying to advance our understanding and ability to treat lung cancer is more research, but I would say beyond that, we need to increase the participation of patients in this process. Only 3% of cancer patients of middle age participate in clinical trials and even fewer in a higher age group do so. I wouldn't say that that's the case for our patient population here, but it's important to recognize that this is a very small fraction of patients who are participating to make important advances and that the physicians and scientists who work hard to try to accomplish this would never be able to do it if it weren't for these volunteer patients.

Now in this time of cautious optimism again. *Time* introduced another concept aside from how are we dealing with cancer and how are we developing new drugs for cancer, a more global issue of what advances are there in administering drugs in all of medicine. In fact, in just a few months ago, one of our scientific journals, *Science*, had a whole story specifically on cancer treatment and discussing the idea of personalized cancer medicine. But what's striking again is that cancer treatment has always been personal and, in fact, Sir William Osler, who is one of the most renowned physicians in American medical history stated quite early on if it were not for the great variability among individuals, medicine might as well be a science and not an art.

Now, of course, there's always artistic aspects to our patient care, but what we're trying to achieve at this time, is to make it more scientific in order to better personalize it than we can right now. We've always tried to treat patients as an individual, and we've done this by asking fundamental questions as we evaluate and meet with the patient. Does the patient want treatment? Will treatment help this patient and lead to a better quality of life as opposed to no treatment? And if we've decided treatment is going to work, then which one should we use?

Now, we make these decisions based on results of clinical trials and agents that are used in groups of patients that are similar to the patient in the room. The dose that we use and the schedule that we use are also based on those clinical trials and occasionally if we've had the opportunity to do so, some additional trials that let us learn more about how to get the right dose in the right patient and some advances in this field occurred in the last half of the 20th century. Observant physicians noted that sometimes unusual responses to different drugs could run in families and when they were able to determine the fundamental basis for that, the field of pharmacogenetics was born. And one very good example of successes in pharmacogenetics is a perhaps little known fact that about 10% of persons of European ancestry don't get any relief of pain when they take Tylenol III, but if they take a similar medicine like Percocet it works just fine. Through some careful investigations physicians and scientists were able to learn that this was related to a deficiency of an enzyme called CYP2 D6. A key point of all this is that personalized medicine research is really best performed on patients not on animals.

Now that I've given you a little bit of a sense from where have we come, the next question with personalized medicine and lung cancer is where are we going? I think these days if you're one who subscribes to the hype, you've been promised that something along the lines of what Dr. McCoy could accomplish in *Star Trek* and if you're aware of this film at all, "Gattaca" which I really got a kick out of it. It's a futuristic science fiction film about an era when your genes can tell us everything about you and it came out just a couple of years before sequencing of the human

genome was completed and I think it had some important cultural commentary on these issues of how much of what we are is our genes vs. our environment and our spirit.

Despite all of the hype about this issue, the goal for the distant future is very clear. We want to be able to put the correct drug at the correct dose for every patient every time and with that get the maximum efficacy out of a drug with the minimum toxicity or basically through all this careful research take our not-so-magic bullets and actually turn them into the magic bullets that Dr. Ehrlich first thought of.

Why is this reaching sort of a confluence of excitement today? It's because of (1) the advances in computer science and information technology that are revolutionizing all aspects of our lives. They also are revolutionizing science and along with that the recent completion of sequencing of the human genome means that we've actually been able to fuse these two advances together – the advances in genetic science and the advances in information technology – into a field that we'll loosely refer to as Omex. The capacity to use all of information technology and apply it to collecting massive amounts of information, whether it's sequencing your complete genome or identifying every protein floating around in your blood at a particular point in time. We now have the tools where we actually can handle these large quantities of information, but the fundamental question is – how do we use that to help our patients? And so I raise the last question of what can we do today to improve treatment specifically of lung cancer?

Dr. Salgia told you a little while ago about scientific approaches to personalizing cancer therapy, focusing on the tumor, identifying specific targets for which we could develop drugs or for which we already have drugs, and using our study of the tumor to perhaps identify what's the best drug for treating the tumor. But that raises the issue of what is the best drug not just for treating the tumor, but perhaps at the same time for the patient. We have to ask the question of, even if a drug is good for a tumor, is this patient going to handle the drug normally? Are we going to achieve blood levels that are necessary to have the effect on the tumor? Will the levels be so high that the patient is exposed to dangerous side effects, or does the patient already have underlying in their system a special sensitivity to the side effects of the drug when it reaches even normal levels?

One example of how we've been able to make advances in understanding the patient's special circumstance has been conducted primarily here at the University of Chicago, of course, with many other centers making important contributions with the chemotherapy drug, irinotecan, also known as CPT11, and I'm going to refer to it as CPT11 from here on out.

Now, I want you to know, I have to make this statement that I'm not trying to promote the drug in any way. It is not approved by the FDA for the treatment of lung cancer. However, it is commonly used in treating small cell lung cancer, and sometimes it is used in non-small cell lung cancer as well.

The concept here is that one dose does not fit all and that our magic bullets under certain circumstances might not be so magic. And what I demonstrate for you here is data from a simple experiment. You take the same dose of drug and you give it to a bunch of patients. Then you collect blood at different time points after the patient receives the drug and detect the levels of the drug in the patient's blood.

Now, normally what you would expect to see, is a relatively narrow distribution of drug

levels in patients. Almost everyone indicated on the Y axis by the number of people and then on the X axis the actual concentration of blood. Almost all people have a relatively narrow range of concentrations and that's a sign of a drug where one dose could fit all, but oftentimes and as was the case with CPT11, we can see a small population of patients who have higher than expected levels of drug in their system and perhaps another cluster of patients who have much lower than expected levels of drug. A key point is that this variability is normal, and it's seen not just with CPT11, but with many different drugs.

This normal variability has important consequences. The average group of patients, who will have similar results to most patients in the early trials, will, of course, fit into this group and this is the way we develop drugs around the average person, the average person's response to average person's toxicity. But folks who are at this end of the spectrum, have higher than normal levels of drug in their blood and might be at increased risk for severe side effects by having too much drug in the system.

While patients over at this end might be receiving too little drug, and it might even be too little to have full effect on their cancer. So without looking at drug dosing and drug response at this careful of a level, for example, we might be missing patients who don't have a tumor that's resistant to the drug, it's that their system is doing something to the drug that keeps it from getting levels necessary to have an effect on the tumor. Now, oftentimes this variability might be related to age, sex or body size, but many times it has nothing to do with these factors.

In the case of CPT11 with ten years of clinical research on people as well as laboratory work from the genetic side, we've been able to identify a certain gene known as UGT1A1 and certain variations on that gene that are very common in the population. Without going into any detail, let's call one version of the gene 7 and another version of the gene 6, and, indeed, the model example that I just showed you to some extent does line up with these genes. So if you were to have two copies of the 6 type gene, you'd likely have lower levels than the average group of the drug in your system when we measure it. If you have two copies of the 7, you have higher levels and if you have one of each, then you might tend to be more in this average range.

A clinical trial performed here at the University of Chicago demonstrated the significance of this very clearly for CPT11, where you see that patients who had the 7/7 version of the gene were much more likely to have a severe side effect of very low white blood cell count after receiving the drug whereas those who were 6/6, no individual in that group had white blood cell counts as low as these folks who were at risk for severe infection and having to come into the hospital for treatment.

Indeed just a couple of years now, the FDA approved the first pharmacogenetic test for looking at the 6 and 7 variations of the UGT 1A1 gene before giving a patient CPT11, and this advertisement has been featured prominently in many journals that oncologists read in the last year to try to promote our using this test more frequently as a way to perhaps help to keep some of our patients from suffering some severe side effects. So we do have pharmacogenetic tests available today. I have tried in appropriate circumstances to use this in my practice, but it's not fully useful yet. There's much more that we really need to know about the relationship between the gene, the drug, the side effects and the levels in the system in order to really use this test to its fullest capacity. The question that is being asked in the clinical trial right now conducted by my colleagues at the University of Chicago asks the question about the group who have 6/6 and who likely have lower than average levels of CPT11 in their system over time after they get the drug. We are asking the question: Can these patients handle a higher dose than the average recommended

dose safely? And then – is this going to lead to better results in the treatment of their cancer?

More broadly speaking, my own personal research interest is to figure out how we collect this information and how do we use it to advance development of lung cancer treatment. In clinical trials that we have going on here at the University of Chicago right now, some folks who have been attending these sessions might even have participated in some of these studies. For example, in this one, we've been asking the question if the severity of the skin rash that is commonly seen when someone takes Tarceva or Erbitux, if that can help us to separate patients from those who might be more sensitive or more resistant or more overdosed or more underdosed than the average group. The study we're doing right now involves Erbitux.

Another study that we have ongoing right now involves a drug that Dr. Salgia just spoke about, sorafenib, the brand name is Nexavar, and ask whether the blood pressure changes, the increases in blood pressure that we often see with drugs like Nexavar and Avastin, can this be used as a measurement that would help separate patients and tell us whether we're dosing them properly, overdosing them, underdosing them, or perhaps choosing the wrong medicine.

So what can we do today collectively here to improve treatment of lung cancer?

My assistant in the laboratory was wondering when I practiced this talk why I kept using these test pilots here as my example of people participating in clinical research and a few of my patients are smiling because they know that this is my sort of personal spiel.

Oftentimes patients when they first hear about participating in a clinical trial they say, "You mean I'm going to be a guinea pig?" and my answer is no. We have to change the way we look at this. You're not a guinea pig. I think you're more like a test pilot. I don't want to sound too corny about this, but when you think about the analogies, a guinea pig looks like a harmless, helpless creature that is just waiting for its owner to do whatever it will, bring it food, bring it water, take it out of the cage, basically has no control over its life and how it's being treated. Test pilots on the other hand, have the very expensive piece of new machinery, an important new plane. In our case it's new drugs. They have a ground crew. You see members of your ground crew here today -- nurses, our data managers, the other physicians who are looking out after you -- and these gentlemen are very brave, they're pioneering and they're in control. They take this plane out for a test flight. They communicate with the ground crew every step of the way to make sure that any signs of the first thing going wrong, they know about it and the group as a team can make a decision about whether we keep flying or whether we should bring it down for a safe landing and perhaps get a new plane.

With that concept in mind I want to suggest that either as a patient or as a concerned friend or citizen, when you know someone who has been diagnosed with cancer or has had a change in their condition that perhaps they should think seriously about participating in a clinical trial. A comprehensive list of clinical trials for treating cancer is available on the National Cancer Institute's Web site. When my patients ask me what's going on elsewhere, this is where I go. You have all kinds of search criteria that you can put in in terms of the type of cancer you have, the stage. You can even put in the zip code of where you want to be treated. If you're local and you just want to know what's going on here at the University of Chicago, this is our URL. We have a similarly comprehensive page of the clinical trials that are available here at our institution. And if you're not Web savvy or don't have access to a computer, Joanna Griffin is a wonderful person who knows

this information, answers this telephone and puts our patients in touch with us about clinical trials in which the patients are interested.

To conclude, the question about what can we do today to improve treatment of lung cancer, you've heard about throughout this month. It's not just about the research, it's about finding a treatment team you trust. It's about utilizing all the available resources. It's about networking with advocates for quality care and improving research and seeking opportunities to participate in this whole process. In that spirit led by Dr. Salgia and the many people participating in the system, I'll conclude with this concept and I thank you all for your time.

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