

NCI 2007 PRE-OP THERAPY IN BREAST CANCER
39_SESSION 6_8 - ZUJEWSKI

DR. KATHY PRITCHARD: Thank you very much, Don. I'd next like to introduce Jo Anne Zujewski, who's Head of Breast Cancer Therapeutics at the Clinical Investigations Branch at CTEP. Welcome, Jo Anne. Or maybe you've welcomed us?

DR. JO ANNE ZUJEWSKI: I'm really happy to be able to participate in this conference and I will try to keep it under 11 minutes if I can, because I know everyone's going to be hungry. And one of the advantages of coming last on a scientific program in a formal presentation is that a lot of what I do have to say has been presented very eloquently beforehand, so the talk that I was going to give I'm not going to give and I'm going to bring up some points of sort of where we go for the future, based on what we have seen in these last few days.

Now I'll need to figure out... [Brings up slides] I have to start with a disclaimer because I work for the National Cancer Institute, in the government, but this isn't U.S. government work per se. My opinions are my own opinions as a person working in the field and they're not meant to be representative of the U.S. government. And I wanted to say that so that no one comes up with, well, you said we should do this, where is the money -- I shouldn't say that, but, it's true. (Laughs)

Okay, considerations for future research. I wanted to address four issues. One is, what is the problem we are trying to solve? And in this, I'm going to go back to some of the opening talks we had with Dr. Wood and Dr. Hortobagyi. The second thing is, what are we doing today? And that's just going to be a brief review, again, of everything -- well, not everything, but of some of the things that you've heard over the next two days -- the immediate next steps and then the big picture.

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So, the first question is, what is the problem we're trying to solve? And it really is one of personalized medicine. You know, we're trying to tailor therapy, the right treatment to the right person. And that's a lofty goal. I think it's an achievable goal. It's going to take us a while to get there. But I think Dr. Wood did a little bit more... better of a job in outlining specific goals that we can look at. Because it's one thing to say, "personalized medicine"; it's another thing to say well, what do we mean by that?

And I really liked this hierarchy -- no recurrence of the cancer, no evidence of having had breast cancer, no evidence of having had treatment for breast cancer, no acute toxicity of the therapy, and no late sequelae of the therapy, because this really is the clinical end of things. So sometimes we get all caught up in understanding the biology, which is extremely important, in trying to image and know a particular patient; but even if we can detect a pCR or increase of pCR, we don't know if we're really going to achieve one of the goals on this.

And so I think it's important with every trial that we do to make sure that we're really thinking of the outcome on a clinical end. And it's a little easier for this audience, since we're all in the clinical research area.

This is a slide that you've all seen in Middlesex Hospital and I wanted to show it so that we can review sort of where we've been over the past few decades. And what it shows is patients who didn't receive any specific treatment for their breast cancer -- it was a select series over, you know, about 100 years I think, maybe not quite that long, where patients basically had supportive care for probably locally advanced and metastatic breast cancer.

And the thing that we learned from here is that, you know, some people can live a long time with their disease. So those patients potentially would be able to be cured by

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surgery alone and mastectomy. And our goal was to push this curve, if you will, up to what a normal survival would be, which is the top curve.

Now, this is a slide I use from Soon [Paik] and I think it's really helpful because it points out how we got where we are today and we really are in a good place. So people who had no surgery had a survival curve that's modeled there -- mastectomy would cure some, chemotherapy and hormonal therapy would cure others. Chemotherapy and hormonal therapy and targeted therapy would cure others. So we've been really focusing, drilling down hard, on the no recurrence. And I think that's important.

But each incremental step assumed that no patient is cured with the previous step. And that leads to the problem we have today, is that we have significant over-treatment and there's a necessity to conduct large trials to demonstrate a small benefit.

And I really want to talk about the over-treatment because in the recent St. Gallen conference, they did a survey of people in the field on the Web and wanted to know what the most important translational research objectives were. And the number one objective, by far, was identifying patients who don't need additional chemotherapy.

So, we're pretty convinced that we can tailor therapy for some people, and we have to make sure that we can do it by taking away other therapies and making sure we don't lose sight of the "no recurrence of cancer", and that's very hard, because the studies are very large and taking away therapy is always harder than adding more therapy. But, it really is where we are today. And this is just the price of our progress.

Now, the next thing I wanted to talk about is really, what are we doing today? So this is just examples of the CTEP portfolio, primarily. Not every study, because I can't do

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every study. But I wanted to say that, concurrent with the progress that we've been making in terms of adding incrementally small benefit, we've entered the age of molecular medicine and molecular profiling. And I think this is, as everyone knows, really important because we can address subtype-specific questions.

And, in the neoadjuvant setting in particular, we can select therapies for future research. Historically, we used the metastatic setting to select therapies that were promising, to bring them into the adjuvant setting. And that paradigm still exists. But today it's very difficult to tell what a phase 2 metastatic setting trial of response rate really means, because the patients, even if they're first-line metastatic, could have had between zero and four or five prior chemotherapy regimens in the adjuvant setting. So, it's no longer as helpful as it once was in determining, you know, some of the resistance patterns.

And so I think using a neoadjuvant approach may be the one way that we're going to be able to select different therapies to go on to these confirmatory targets. And there's some risks in that that I'll talk about a little bit. And in all the trials we have the discovery of targets. So I don't want to under-estimate the value of looking at the biology of these particular tumors as we move forward.

The first trial I wanted to mention was the ACOSOG trial [ACOSOG-Z1031]. I look at this as a selection design. It does go on the goal of "no recurrence of the cancer". But it's also trying to back off of -- "no acute toxicity of the therapy", "no late sequelae of the therapy", because the goal of this trial is to pick an A.I., if there is one, that we can go against chemotherapy in a prospective randomized trial -- to try to safely back off; you know, that's one of the goals, not all of the goals.

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I think that this trial was possible because all these agents are commercially available. It wouldn't be possible to do this type of a trial very easily, if at all, when you're doing new agents that are more interesting because people over-interpret these small results. So, companies are not going to be that willing to put their agents against other companies' agents in a selection design because it's under-powered.

But I wanted to bring that up because I actually think that would be very, very helpful for us as we move forward in being able to test new agents in the neoadjuvant setting -- sort of that window approach. And, unfortunately, some of the agents -- not all the agents -- are made by the same company and they don't want to, you know, bank one agent against another. So, that's more of a global issue we have to handle.

The ACOSOG trial is ... I'm sorry, let me go back. This trial [ACOSOG-Z1031] is a trial that we have in the neoadjuvant setting for endocrine tumors. So this a subtype of ER-positive.

The next subtype that we're dealing with is HER2 positive. And this is the ACOSOG study [ACOSOG-Z1041] -- we've been over it twice before. But its goal, really, is "no recurrence of the cancer". And it is also trying to back off from no "acute toxicity of the therapy" and "no late sequelae of the therapy".

And I think it's really interesting that the German group presented data with using trastuzumab and epirubicin concurrently, with no apparent early safety signals. So I think this is an important observation -- that we might be able to make our therapies safer by different schedulings, or even switching the chemotherapy. And obviously we're not there yet, but I do think that it's an important study to follow up on.

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The next study that I want to talk about is the CALGB study with HER2 blockade that we'll be sponsoring. It's not yet finally approved in its protocol form, but it will be moving forward. And this one, in addition to the molecular markers I think, are really, "no recurrence of the cancer". You know, it may be that a tyrosine kinase inhibitor is going to work better than trastuzumab, a biologic, and be safer in terms of the heart -- we really don't know that. In the third arm, where we're combining trastuzumab and lapatinib, and we're definitely trying to decrease recurrences; and, again, every time you do that it sort of adds to toxicity, but I think this is an interesting study that I'm looking forward to see the answers of.

And in the triple-negative group, we've got a DNA-damaging agent where the CALGB, again, is going to be using paclitaxel and randomizing to carboplatin versus not, and also looking at the bevacizumab -- trying to look at biologics.

And this study, again, is, "no recurrence of cancer". And this study I'm going to come back to again because we are using the neoadjuvant response sort of like a screening phase 2, you know -- if the carboplatin looks really promising in an early pCR response rate, the plan is to move forward in this population in a randomized clinical trial. And when I get to the big picture part of it, I want people to think about, are we really going to be able to accomplish that?

Anti-angiogenesis is sort of a combination of chemotherapy and biologics. I added this because this is the NSABP-B-40 trial. It's an unselected population in terms of triple-negative versus ER-positive. But, they're looking at different chemotherapy regimens, and, along with bevacizumab.

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So I think this will be very helpful for predictive models, but it also helps us understand that we may not know the target, and we may not even know if we're targeting the blood or the tumor, but we still are going to be able to use this setting to develop predictive markers for outcome. And we have to be careful about the outcome we're trying to predict, which should really be disease-free or overall survival.

Now this, again, because it's adding on therapies, I think is a "no recurrence of the cancer", primarily, along with the biology. All of these are "the biology".

And this is a Cooperative Group study, although it's not an NCI-sponsored study -- it's the German group study [GeparQuinto]. But I really do like the idea of seeing if we can use early response to therapy, or early imaging, or, as Dr. Berry talked, in sort of I-SPY, to direct at an individual patient. And I don't know if that's going to be possible or not. But I liked the design and I think that's where we have to be heading, so we don't just keep incrementally adding, adding, adding. And this, again, I think is a setup for "no recurrence of the cancer" because they're picking a resistant group.

So, the next thing I wanted to talk about is the immediate next steps. So, we have all this information. We've made a lot of progress. So where do we go from here? Well, the one thing that was pretty clear is we have to do it together. And I'm very excited to say that the Breast International Group, the Breast Cancer Intergroup, and the NSABP have been meeting over the past two years to try to coordinate our global efforts in breast cancer.

And I think this is really a pivotal moment. It's an important moment. And, amazingly enough, I shouldn't say this (Laughs), but we really are getting some things done. And

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here's the first thing that we think we got done. We have to implement it now. But we did incorporate specimen collections standard operating procedures.

I'm not going to read this to you, because it was presented in an earlier slide -- it will be Web cast and video cast, video archived -- so you'll be able to look back at it. But what it says is, we need to improve our diagnostics and we need to do what we need to do today so that we can go back and look at these studies. And what the Groups decided to do is at least at this point look at their own SOPs, append them to their protocols, and try to move forward to this kind of an approach.

And I think this is important because I suspect that the fastest way we're going to make progress is prospective validation of predictive factors in "retrospective" clinical trials. But that means you've really got to bank, and you've got to bank well, and you have to have robust assays.

And this is a ... I don't know if Soon is still here, but he has said repeatedly -- and I agree with it -- that the diagnostic people have to develop technologies for the lowest common denominator, because we can do something really fancy in the lab -- and I think that's great for drug discovery -- and we can control a neoadjuvant setting, and we can get what we need to know for gene discovery, but if we're going to translate it, it's got to be easy. So, we can say we want everyone to collect samples in a given way, but getting it to happen is a huge issue.

The next thing I wanted to plug is our STEEP... system -- STEEP system. Cliff [Hudis] coined the name just over the weekend -- I think it was Saturday. And what it is is a standardized definitions for efficacy endpoints in neoadjuvant breast cancer trials. We've done this for adjuvant breast cancer trials. A group of us met over a year from all the

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North American groups -- we had review by the international Groups as well -- to try to standardize endpoints in the adjuvant setting.

And that paper will be coming out. What we agreed to do on Saturday is standardize endpoints in the neoadjuvant setting.

And what I have here is I think from Dr. Hortobagyi's talk -- what a pCR is. In order to standardize endpoints so that we can look and do meta-analysis across trials -- it's not even as easy as deciding which one of these four different opportunities would be a pCR. You've got to decide, you know, what is going to be the events that you're going to capture. Are you going to capture DCIS? How much DCIS? Are you going to measure the tumor size? Are you going to count the number of nodes you did? Is one, single, invasive cell going to be counted or not? You know -- in an earlier talk, we had all the different ways you could measure pCR.

So, this group is just going to be starting, but we're going to tackle that, you know -- We're going to define events. We're going to standardize terminology endpoints. And this will at least allow us to move forward where we're all talking about the same thing and using the same vocabulary. So, that's another next step.

So, the big picture. So the big picture is, how will we get from pathologic complete response to changing practice? And I think this is actually, you know, a real challenge that we have to think of.

And the first question -- I don't have much to say here -- is pre- or post- op [tx] sentinel lymph node biopsy. How can we answer this question? I mean, obviously this is

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controversial. It's important because we don't know what to do with local therapies in today's treatment.

Some people think some day we won't have to look at nodes because everything will be predicted in the primary tumor so you don't actually need to do the sentinel node biopsy. But trying to think about how we can quickly, easily, feasibly answer this question, I think, is a challenge. So that's a challenge for the audience. One of the outstanding questions.

The other outstanding problem we have to deal a lot is confirming surrogates in prospective studies of clinical outcomes. And when Don [Berry] talked, I quickly looked at my slides to see if I took out all the "surrogates", and I didn't -- I still have the "surrogate" in here. But I actually think this is what I'm trying to do -- is pCR going to be a surrogate for anything, and, if so, what? And I think we run into a real problem with early interpretation of results.

So, for example, if we have an increased pCR rate in the triple-negative trial, will people really randomize to a phase III adjuvant trial to go on the no-platinum arm? And I think, you know, that's a problem, but it's necessary. You know, we know that platinum in the metastatic setting has a higher response rate; a Cochrane analysis has been done showing no improvement in progression-free survival in metastatic disease.

There's a suggestion in a randomized control trial that, in spite of really good evidence in the pre-clinical models that platinum and trastuzumab are synergistic, a randomized trial in the metastatic setting did not show an improvement in progression-free survival with the combination of a taxane and trastuzumab and a platinum.

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So, I want to be careful that we don't incorporate toxic therapies too soon without doing the randomized trials, while really understanding that, because of our culture and the fact that we treat prognosis, that we're going to want to give these people "the more is better".

One of the potential questions I have behind that is, should we nest the neoadjuvant studies? And this truly is a question. You know, if you do a study where you have adjuvant and the same treatment given either adjuvant or neoadjuvantly, you overcome some of the problems. You know, one is that there is less selection bias. There's still some, because we select people we give neoadjuvant chemotherapy to.

It would allow, potentially, for concurrent validation, because it would be the same trial, and potentially more robust diagnostics because we can work them out simultaneously. The patients that would have been in a neoadjuvant trial can just participate in your adjuvant trial. So, potentially it would also save resources in terms of patient selections because you wouldn't have to do two studies, you could just use them. But, it's complicated. It sounds easier than it really would be. But I think we're working on there.

This is a problem we're facing today -- and it's, what do you do if you do not get a pCR? So we know that getting a pCR is a really good thing. We know that if you don't get a pCR it's not as good, but it's not necessarily bad, because some people who don't get a pCR do really well. So that gives us this big problem again. And we have the residual risk strategy.

And I think... One of the things I deal with is the problem of "more of the same". So what we want to do, as oncologists -- is, if we have a patient and we've given them AC followed by Taxol, and we do surgery and we get the staging back and they've got five

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positive lymph nodes, we want to do something, because we know that that person, you know, has a higher risk of recurrence. So, we use the available therapies and usually, you know, I know people do in the community -- it's capecitabine, it's vinorelbine, it's whatever it is.

But I'm not sure it makes sense to add more of the same when the chemotherapy didn't work. You know, we have in triple-negative disease -- I think people are pretty convinced that you can look for a pCR chemotherapy response in that situation. And if you don't get it with three or four agents of the best available, there's not a lot to say we're really going to help by adding the drug adjuvantly.

And we've heard from Debbie Collyar that patients really hate to get it. And it's a problem, you know, because patients are like, "Oh, now you've got these nodes, what are we going to do?" And it's a problem in terms of relapsing both locally -- you know, what do we do with these patients locally? -- that goes back to the sentinel lymph node problem -- but also systemically; you know, what are we going to do with these people?

I'm very excited about designs where you use proposed randomized trials for post-preoperative therapy. So what I'm thinking about this is, potentially you could select out the good actors by people who got a pCR and, I think, in combination with Soon's data that he presented this morning, there might be a way we can combine molecular profiling and response to chemotherapy to get a select group that we can then use our novel therapeutics after the neoadjuvant therapy. It gives us a potential to run smaller trials.

This is the trial that was proposed -- and I'm going to be really frank and challenge the audience to say, I'm not sure what I would do with this trial, because there's no control group. You know I do think we should look at adjuvant therapy in the high-risk-of-

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recurrence patients. I think potentially, because what we have are targeted therapies, that that might be a better way to go -- with a targeted therapy, or potentially a chemotherapy and a targeted therapy combined together. But in this trial design, there's no placebo. There's no no-treatment group. And it's going to be very difficult to incorporate this into our practice. So, we're going to have to just bite the bullet and understand that people are going to have a risk of recurrence, but we're going to have to include a placebo group.

And whether these... (So that's why I've eliminated... I'm just learning my animation skills... but that's why I've eliminated it in there... I don't have enough animation [referring to slides] to put the placebo up there yet. That's the next time.)

Whether it's targeted or targeted plus chemotherapy, I know these are hard to do -- patients and docs want more therapy if they know they're at risk for recurrence. But this is really the only way we're going to move forward in a way that doesn't defeat our other endpoints.

This is the second-to-the-final slide. Inflammatory breast cancer I wanted to bring up as a paradigm for rare diseases. We're good at looking at large studies, not so good at looking at rarer diseases. So, inflammatory breast cancer is a rare disease, and how do we study rare disease? You know, do we need more basic science, how would we incentivize those? Do we best study them in a registry? Do we do international randomized trials?

And I think this is a really important problem because, as we keep subtyping breast cancer, we're going to have more and more rare diseases. So we really have to figure out how we're going to test rare diseases... rare diseases in breast cancer. And I really don't

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know how to do that. I do know it's going to be a partnership with everybody else... with academia, industry, government, and advocacy.

And that's one of the reasons I'm happy to have this kind of a meeting because I think it really brings people together to start thinking about the hard questions, so that we can make sure our early work goes forward. Thank you.

DR. CLIFFORD HUDIS: Thanks, Jo Anne.