

NCI 2007 PRE-OP THERAPY IN BREAST CANCER
32_SESSION 6_1 - PAIK

DR. ERIC WINER: So, the next session is on research issues. It will prove to be entirely non-controversial, and will be chaired by Kathy Pritchard and by Cliff Hudis, both of whom are known to you all, so I'll spare you the titles.

DR. CLIFFORD HUDIS: So, some of you might actually wonder why I'm up here, after my comments yesterday. I just want to reassure everybody... But, actually, the concern I expressed yesterday relates to sort of general practice. I think that what we're about to talk about in this session is really the crux of the agenda for the scientific aims that we all share. And there are a whole series of exciting talks focused on what we can actually do with preoperative specimens, which I think is really the point.

So, with no further ado, I'm going to invite Dr. Paik to join us. He's the Director of the Division of Pathology for the NSABP. He's going to talk about the importance of getting preoperative research biopsies.

DR. SOON PAIK: Good morning. It's a great honor to be here to give a presentation. So, I guess everybody knows the importance of obtaining tissue for research.

So, what I'm going to do today is, in specific trial [NSABP-]B-27 -- how we are using the collected tissue samples to understand the kind of puzzling aspect of the clinical data. So, there are obviously available tools for prognostication of patients in adjuvant setting that can identify high-risk patient.

We know that from a variety of studies, the high-risk patient derive the maximum benefit -- or greater benefit -- from chemotherapy. However, these tools are kind of probabilistic, in that the tools cannot really tell who actually benefited from

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chemotherapy after getting the therapy, and who need more than chemotherapy after chemotherapy is administered.

So, for example, the OncotypeDX assay, based on 16 cancer genes, is a linear predictor of the distant recurrence for the... ER-positive, node-negative, tamoxifen-treated patient, with increasing score correlated with the poor outcome. And we have demonstrated that in [NSABP-]B-20, that the increasing Recurrence Score also correlates with the increasing benefit of the chemotherapy.

However, even looking at this curve, although we can kind of tell the residual risk of the patient who got chemotherapy at high risk, we don't actually know which patient actually derived actual benefit.

On the other hand, in the neoadjuvant setting, pathological response provides a patient-specific kind of in vivo assessment of tumor response. However, it's not a perfect surrogate for survival endpoint, in that, in B-27, even the doubling of pCR rate did not really translate into... doubling of the reduction of the mortality. It does not provide baseline risk for the assessment. So, you cannot just use pCR for prognostication.

So, in B-27, as you know, in the adjuvant setting, randomizing AC or AC followed by paclitaxel, the pCR was an excellent surrogate for survival outcome, with highly statistically significant result. However, you can see that the no-pCR patient also has a fairly good outcome.

So, although there was a doubling of the pCR rate when you add paclitaxel to AC, when you actually look at the clinical outcome, there was no difference in these patients in the survival endpoint. So, why is that?

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So, it looks like there is really no perfect tools that we can use either in the adjuvant setting or in neoadjuvant setting to really make a patient-specific decision-making.

So, the crux of the question is, naturally, is pCR a valid surrogate endpoint?

We can kind of look at the B-18 data and do a simple, mathematical extrapolation into B-27 to understand what's going on. So, if you look at the B-18 data in the AC arm, there was about 15 percent complete pathological response -- they had about 90 percent five-year survival. And the rest had about 75 percent. So, you can kind of calculate the survival of all patients at five years to be about 77.25 [percent].

So if you extend that to AC-->T arm, with doubling of the response rate, you can see that the extra expected difference between the survival endpoint at five years is only about two percent. So, the trial itself was not really powered enough to be able to tell this difference. Now, if you keep on doing that exercise with increasing pCR rate, you can see that to show about five percent difference, you actually needed about 50 percent pCR rate.

So, it is probably the reason that we have such a small -- expect such a small -- difference is because the non-pCR group actually has a fairly good prognosis. So, when they are not responding to chemotherapy, why is their survival so good and not this steep?

And our hypothesis is that it's a problem of patient selection, in that this non-pCR patient is mixed with a good-prognosis patient -- inherently good-prognosis patient -- who doesn't really gain much benefit from chemotherapy. Similar to what Dr. Gianni has shown yesterday with OncotypeDX assay.

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So, in order to address that hypothesis, we did a retrospective analysis of the B-27 core biopsy samples. Now, this trial actually is, in some sense, tragic in the sense of research because of the ongoing debate of the genetic issues and informed consent issue when we launched this trial. We couldn't really incorporate tissue collection into the main protocol. It had to be separated out. And while this is being debated and launched, almost one year has passed.

And, also, B-27, as a successor of B-18, following Fischer doctrine of minimal perturbation of the kinetics in the tumor, originally FNA was recommended over core biopsy. So, by the time the B-27.2, which is a core biopsy protocol, was launched, we lost a lot of patients.

And initially planned markers included the garden-variety of IHC markers; but technology has evolved. So, in the end we actually had to develop a whole new method to... a gene expression profile of the paraffin block.

So, in the end, after about five years of effort in the lab, we were able to develop a method to profile the paraffin block with Affymetrix GeneChip. So, we started with one section of the paraffin block... core biopsy; and I extracted about 100 nanograms total RNA, amplified it using Affymetrix GeneChip, hybridizing it to result on about... expression profile of about 60,000 genes.

And, what I'm going to show you is a fairly preliminary look at the data -- not really optimized analysis. But we used a Prediction Analysis for Microarrays and Supervised Principal Components analysis to predict ER status, pCR, and outcome.

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So, now, let me just go directly into the results. So, if you disregard the pCR and simply regard it as a survival endpoint trial, and ask whether there is a gene signature that predict outcome in this trial, and there is.

There's about 90 genes that can actually robustly segregate low-risk versus high-risk patients, half and half. Obviously, this is a continuous variable -- I'm just showing you the immediate color of the data.

And now, what happens to this profile when you look at only non-pCR patient? Remember, our hypothesis is that non-pCR patient has a fairly good outcome because it's contaminated with fairly... inherently good-prognosis patient.

That's exactly what it shows. That if you look at no-pCR patient and you look at the gene expression profile, about half of the patients actually has a low-risk profile, which has a very good outcome, compared to the patient with high-risk and no pCR.

So, I think we answered the question that the reason that we have no survival difference... we couldn't detect survival difference, even after doubling of the pCR, was because this no-pCR group is contaminated with good-prognosis patients.

Now, suppose if we actually conducted a trial with highly selected, poor-risk patients. And then here is an original trial, with no selection. And here is expected outcome with high-risk-only patient, based on gene expression. You can see that the expected difference for doubling of the pCR is much higher -- about twice higher -- a four percent difference, when you actually -- if you have conducted your trial with high-risk patient.

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Now, interestingly, in no pCR..... uh, a low-risk patient, the pCR really didn't seem to matter on the prognosis. But, obviously, the patient number is very small to make much conclusion here.

The important finding, I think, is that, in high-risk patient by gene index, if they had pCR they had much better outcome than the no-pCR patient.

So, if you actually combine upfront gene expression profiling for prognosis, and then use the neoadjuvant setting to assess the in vivo response, then you can actually identify these high-risk patients who didn't respond to chemotherapy. So, they actually become probably the good candidate for post-neoadjuvant trials for targeted therapy or other therapies that Harold [Burstein] mentioned yesterday.

Now, can we predict pCR with gene expression? I think a lot of groups have tried it, and my answer is, I think probably we cannot really accurately predict it. So, if you simply look at the pCR rate according to this prognostic signature, obviously there is a higher pCR rate -- doubling of the pCR rate [in high-risk?] -- but low-risk patient also has pCR.

Now, the gene expression analysis that we conducted produced a fairly pristine data because -- although it was done with paraffin block -- because if you ask the gene expression data to predict ER status done by central assay, there is a 96 percent accuracy in predicting ER status. So, the data is fairly pristine.

But if you then ask whether we can predict pCR with the gene expression signature, the accuracy goes down significantly -- only 75 percent. And that's kind of the experience, overall, in the field.

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Now, we can increase that accuracy a little bit better, to 85 percent, if you restrict the analysis to only ER-negative patient; but, again, still, it's not like estrogen receptor, where there is a clear biological difference.

So, this could be because the tumor response is a fairly heterogeneous phenomenology influenced by many things in addition to the gene expression pattern within the tumor -- maybe the dosing issues, duration issues in the patient, and the drug distribution issues that requires to be calculated together with the gene expression status of the tumor.

So, in B-40, we are actually mandating the pre-treatment core biopsy collection in three forms -- RNAlater, so that we can have a very pristine gene expression analysis and there can be... RNAlater is a solution that allows collection of the tissue at room temperature, and shipped it at room temperature, and still preserves very good quality of RNA.

And we actually found that, in B-27, there is a bias in the collection, in such that the pathology department usually refuse to send the core biopsy from patient with a pCR, because that's the only block that contains the tumor. So, if you look at my analysis, the pCR rate is significantly lower than the actual trial because of that fact.

So, we learned a lesson. So, we are actually collecting additional cores in formalin, so that we will have a guaranteed research paraffin block that can be used to validate what we find in the fresh-tissue RNA expression profile and also optimize it for the routine practice. And we are also looking at in vitro chemosensitivity assay by collecting tissue in Hank's buffer, so that maybe, instead of doing... going through the pCR, maybe we can replace that with in vitro chemosensitivity assay in the end.

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So, in conclusion, I think the gene expression analysis of the pre-treatment core biopsy in B-27 provided a biological explanation of the puzzle. And the combination of gene expression and the pCR in the neoadjuvant setting may identify patients who need more than chemotherapy; and we want to validate that in collaboration with the ECTO and NSABP-B-40 trials. Thank you.