

NCI 2007 PRE-OP THERAPY IN BREAST CANCER
15 SESSION 2 TALK 5 - GARBER

DR. LARRY NORTON: The next speaker, Judy Garber, from Dana-Farber.

DR. JUDY GARBER: So, I've been given the privilege of speaking about another tumor subtype for which there is not very much data; and, in this case, I have to thank Lisa Carey, who probably should be giving this talk and who shared some of her slides with me, since she's certainly done more work than I have.

So, I think we've all been aware that there were ER/PR/HER2-negative tumors that probably came into definition when HER2 was defined. And there's the basal-like subtype of tumors that were defined by microarray analyses. And there's discussion very often, some of it heated, about whether these are overlapping groups or equivalent groups. And they are NOT equivalent, but they are largely overlapping.

Some very nice work by Chuck Perou's group has tried to take the microarrays -- which are not ready for primetime in all areas since they're done on frozen tissue -- and tried to look at markers that could help distinguish those within the group. In this case, immunohistochemical markers, but certainly they've also identified -- and I think I neglected to include a slide -- showing some of the molecular markers that they've identified in this subgroup.

Here are many that can be measured by immunohistochemistry -- trying to distinguish the basal-like subset. And you can see that in this case, and also from the microarrays, that potential targets like EGFR and c-kit have been part of the picture. p53 mutations are common; vimentin -- very common... If you're looking for other ways to distinguish. Now, in our data, it turns out that the CK 5/6 marker is not very helpful in discriminating between basal-like and triple-negative tumors since it's so commonly positive, but there's variation in the literature.

And there's been an attempt now to recognize that if this is a subset, maybe you can figure out who's at risk to get it. And, unfortunately, in this lovely analysis by Yang, you

PRE-OP THERAPY IN BREAST CANCER
15 SESSION 2 TALK 5 - GARBER

can see that many factors that we've talked about as breast cancer risk factors for a long time are significant, on this slide in green, and those are largely in all luminal A, ER-positive tumors and really very little for the basal-like, in this analysis.

Now, they're not very large numbers, so we might do better in the future; and absent from this slide is the analysis that Funmi Olopade has made famous, which is that triple-negative or basal-like tumors are much more common in individuals of African descent -- and why that is true remains an important mystery.

So, here are one of the early analyses that showed that having a triple-negative or a basal-like tumor was a bad thing. And this was from the Sorlie paper using the microarray data to try to look at outcomes -- the red lines on both of these for disease-free... for survival and relapse-free survival are the basal-likes, hence some of the concern about these tumors.

And here's some data on the left, published by Rouzier from the MD Anderson group, showing that within neoadjuvant therapies, though, these tumors are quite responsive.

And some data from Lisa [Carey] from a paper that I think we should all look forward to, coming in *Clinical Cancer Research*, showing that, with a similar drug combination, not quite the same, but similar sensitivity, which we've now seen as a theme throughout the morning -- not uniformly, but certainly in general -- that these tumors should be responsive even without HER2.

These are Lisa's data, too, just showing that this is... well, when there are pathCR's, that in this group you can expect the same effect on survival -- which is a hopeful sign for these as well as others.

Here are Dan Hayes's data. It's nice when everybody's in the audience so they can check that their data are being accurately represented. (Laughter) And here's Dan's data from

PRE-OP THERAPY IN BREAST CANCER
15 SESSION 2 TALK 5 - GARBER

ASCO suggesting that paclitaxel is an important part of therapy for the ER/PER/HER2-negative group. And I think that that comes to mind in data that we've seen elsewhere today, that this is an important segment of therapy, certainly, at this time, outside of clinical trials -- to answer one earlier question.

But the question is for these, which are sort of the non-A, non-B hepatitis of our era -- what are the targets and how can we improve therapy over and above the chemotherapy agents we have, or with the strategies that we have available?

This is a diagram from a very nice review of therapies on triple-negative carcinomas recently published in Lancet Oncology suggesting that we could target some of the things that have been raised in Chuck Perou's work -- the c-kit receptors, EGFR receptors, various other pathways, all looking to cell death.

And the kinds of data that you start to see coming are cell-line data that have asked, what if you target different molecules in these pathways? Do you get an effect on the cell lines, and can you then take that into humans? And if you're going to take it to humans, then, of course the neoadjuvant setting is a good place to go, since you get to do -- as Lisa presented also in the earlier data -- you can get tissue, you can measure things in the short term; of course, generally you don't do that except after metastatic disease trials.

So here are two metastatic studies that have been going on in which cetuximab, targeting EGFR, has been added.

Now, the US Oncology study -- and I thank Joyce O'Shaughnessy for a very nice email explaining all of this -- but she didn't have slides for us -- but in this study they recently did, in 150 women with metastatic breast cancer of various types, they used an irinotecan-carboplatin combination, versus the same with cetuximab. They added cetuximab at progression.

**PRE-OP THERAPY IN BREAST CANCER
15 SESSION 2 TALK 5 - GARBER**

Very similar to Lisa's study in the Inter-SPORE group with, in this case, just carboplatin plus cetuximab, versus cetuximab with carbo added.

And, in this case, in the US Oncology trial, the responses were seen, really exclusively, in the triple-negative group. And that has led them to develop a 50-patient, neoadjuvant, single-arm study in triple-negative breast cancer, and then Lisa's study, which is now in interim analysis.

And here is the proposed CALGB triple-negative schema that will build on Lisa's study, which I think she showed before -- in this case, adding bevacizumab and asking about carboplatin as well, in this case with Taxol.

This is from lovely data shared by Washington University -- Paula Fracasso and her group, who did a phase 1 trial of UCN01, which is a kinase inhibitor -- now, it's not a specific kinase inhibitor -- it inhibits a lot of kinases, I'm told -- and that with irinotecan. "And why irinotecan?" we can ask. But in the combination in a phase 1 trial, they had two partial responses -- these are the photos from their AACR poster showing response, which I hope you can see. I can see it from here. A very nice response in this patient with local disease.

And this has led them to apply to CTEP to do a neoadjuvant trial in triple-negative breast cancer, since that's where the two responders were. So now we're talking about targeting EGFR and targeting kinases in these patients.

We got interested in these because of the link to BRCA1, in that BRCA1-associated tumors are so often triple-negative and start in the basal-like group.

And the question there has been one of biology: Can we use what we know about BRCA1 and BRCA2 to exploit for therapeutic strategies using a different set of information than we obtained from the microarray analyses?

PRE-OP THERAPY IN BREAST CANCER
15 SESSION 2 TALK 5 - GARBER

Here's very nice data from Will Foulkes showing just this -- that the majority of tumors -- the great majority in young BRCA1 carriers -- are ER-negative tumors and they all have a paucity of HER2 positivity, whatever that is about; although there is an increase in ER-positive tumors over time. In the BRCA2 population, the prevalence of ER-positive disease is much more typical for tumors overall.

And these tumors -- the basal-like tumors and the BRCA1 tumor -- share many features. Not only their immunohistochemical characteristics, but they're poorly differentiated, they're cyclin E positive; they also have basal-like immunohistochemistry and they do cluster down here in the basal-like areas.

So, in an institution where BRCA1 function is of interest to a large group of scientists, we try to go forward on this question. Here are some data looking at radiation-damaged BRCA1-deficient breast cancer cells showing some very typical chromosomal abnormalities. These are the same sorts of abnormalities that are seen in Fanconi anemia patients who have difficulties with DNA repair when their cells are radiated. And here's, from Dan Silver, a slide looking at a basal-like tumor not from a BRCA1 carrier, showing these very similar chromosomal abnormalities after radiation.

There are theories and diagrams -- always a good thing so you can have targets -- to ask, why are these similar? Certainly, in work from Andrea Richardson, who's here, there's ample data that most of the basal-like tumors are completely BRCA1-intact. Whether they're functionally intact is another question, but the BRCA1 gene is certainly on and expressed in most of these cells. And it's not clear what BRCA1 loss -- how these are different, whether they really do find a common pathway, but that's the theory that would allow us to go forward with our thinking.

PRE-OP THERAPY IN BREAST CANCER
15 SESSION 2 TALK 5 - GARBER

BRCA1-deficient cells, and BRCA2-deficient cells in fact, have these double-strand DNA break problems when you damage the DNA in specific waves, so, with gamma radiation.

Remember -- these are the tumors, not the normal tissue, fortunately, so they are able to repair the usual errors in their normal cells. And Mitomycin C, which would not be an ideal neoadjuvant agent, but does cause double-strand break repair good for biological systems research.

And every interesting cell-line data, not from our group, that showed that this cell-line, which is BRCA1 minus minus, has unusual sensitivity to platinum -- a double-strand-break-inducing agent -- and not very good sensitivity, in this model, to either doxorubicin or paclitaxel. So, that's a little surprising given the neoadjuvant data we've seen before, and certainly different from other, more typical breast cancer cell lines.

So here we are back with these sort of curves again from Dan Silver, showing that tumor cells that are BRCA1-deficient are very sensitive to cisplatin. Other cells -- in this case, non-basal-like cells -- are not.

And there was also this sort of intriguing data from the ovarian cancer history of BRCA1 and 2 carriers showing that, in data that was always suspect but quite consistent, individuals with mutations with ovarian cancer tend to live longer than their counterparts without mutations; so maybe that was about platinum -- who knows.

So, we put together a small neoadjuvant trial -- and I'll be interested to hear about this in the ethics discussion later in the talk... in the day. This was a trial of women with triple-negative breast cancers of sufficient size, with the usual sorts of measures, who were given cisplatin as a single agent, to ask this question about whether they'd be sensitive to its break effects and whether there were subsets of tumors that would share the BRCA1 phenotype.

PRE-OP THERAPY IN BREAST CANCER
15 SESSION 2 TALK 5 - GARBER

And at the end, after surgery, they would go on to standard adjuvant therapy. Then we did a number of assays. And, to our great relief, there was a pathologic complete response rate with single-agent platinum in that time that was respectable for this group. And there were only, as it turned out, two BRCA1 mutation carriers, although both of them did have pathCR's, which is at least consistent, although it doesn't prove very much.

Age at diagnosis was also significantly associated with response, and we're in the middle of the tissue analyses that might help us figure out the rest of this.

But at least it's so that the other patients who had pathologic complete responses and did not have mutations may share something -- of course, we don't know for sure that it's even got anything to do with double-strand-break-repair effects of the platinum.

So, what about other agents in this group? Well, bevacizumab is the... this is from E2100, so, fortunately, George [Sledge] is here and can attest that ER/PR negative tumors did well in this study. So, in the BRCA1 tumors, there turns out to be an observation of increased vascularity of a particular description.

So in our next study, which Paula Ryan is running, from MGH, we've combined bevacizumab with platinum, remembering to leave enough time for surgery to hopefully keep the complication rate down.

And then our plan to go forward is to look at some very interesting data from Alan Ashworth's group. He's also interested in DNA repair, so thinking in the same way about these tumors and their connections to BRCA1 and 2, where most of this work is done, looking at PARP inhibitors. So, PARP is the enzyme down the next pathway once you've knocked out BRCA1 and 2 and effect double-strand breaks; you then induce single-strand breaks, which this system needs to repair.

PRE-OP THERAPY IN BREAST CANCER
15 SESSION 2 TALK 5 - GARBER

And, here, you can show in some data from Dan that these basal-like cells are also sensitive to PARP inhibitors, so it's tempting to think about putting these together in a trial with the oral agent. And this, too, will follow a nice international metastatic-disease trial looking at PARP inhibitors in mutation carriers that's ongoing now in Europe and opening in the U.S. fairly soon.

So, obviously, we don't know very much about the neoadjuvant treatment of basal-like breast cancers. And if I missed anybody's study, I'm really sorry -- I tried to find them all; but there isn't much.

And they are not a uniform population, and we may be able to sort that out by looking at some of these molecular markers. They are a good system for investigation for biological hypotheses; but I don't think yet that any of the data that we've seen, or any of the theory that we've heard, would inform the non-protocol treatment in the neoadjuvant setting of this subset of breast cancers. Thank you.