SABCS 2013: Notes from an educational session on Triple Negative MBC

Talk by Lisa Carey, oncologist and researcher, University of North Carolina

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Dr. Carey began her talk by emphasizing that triple negative breast cancer is a "title of convenience," as a definition useful in clinical decision-making—In that it defines what targets the tumor *doesn't* have—but she said this title ignores the reality "increasingly clear to all of us of the biologic heterogeneity that is within triple negative breast cancer." This variety of subtypes is what Dr. Carey refers to as the "promise of the future." Triple negative breast cancer consists of at least six difference subtypes of breast cancer, of which basal-like forms about half (49% in this study, but can be as high as 75% for different groups), and about a third (30%) is claudin-low , as well 4 other subtypes (Prat and Perou, Molec Oncol 2010).

- **Tailoring chemotherapy?**

Do we use a different chemotherapy drug in triple-negative MBC than we do in other subsets of MBC? Many studies have explored taxane-resistance (i.e. resistance to treatment with Taxol, Taxotere or Abraxane) . There is a "little bit of data to guide us." A pooled analysis did show that taxanes are better in ER-negative disease, but HER2 status wasn't included—but it should give some confidence that taxanes are a reasonable first line therapy for stage IV triple negative breast cancer.

Are newer agents that act on microtubules as the taxanes do any better than Taxol or Taxotere? Here Dr. Carey was referring to nab-paclitaxel (Abraxane), a formulation of paclitaxel (Taxol) that doesn't require premedication and causes fewer allergic responses than Taxol, as well as to the drug ixabepilone (Ixempra) administered weekly. Each of these two drugs were compared in a randomized trial to weekly Taxol, so this trial had three treatment "arms." Most patients also received bevacizumab (Avastin) as well because Taxol+weekly Avastin had received provisional approval for first-line chemotherapy in MBC at the time the trial was enrolled. In the trial, patients taking Ixempra had less time before their cancer progressed , and while the results for Abraxane were equal to those with Taxol, but there were somewhat more toxicities. (CALGB 40502 Subset analysis)

In later lines of treatment, the drug eribulin mesylate (Eribulin) was compared with capecitabine (Xeloda) in patients who had already received anthracycline (Adriamycin or Epirubicin) and taxanes. (Kaufmann P SABCS 2012). Overall, the study showed these two drugs offered equivalent results, although in a subset analysis, for the triple negative patients, Eribulin appeared to show a benefit over the Xeloda. But other evidence suggests that both of these drugs would be helpful, given as single agents at different points in treatment. Of course, they have very different kinds of toxicities, with lowered counts, hair loss and neuropathy common with Eribulin, and diarrhea and hand-foot syndrome common with Xeloda.

Can chemotherapy be targeted to "BRCAness" characteristics of BRCA+ breast cancers? BRCA-associated breast cancer is almost always triple negative, and many characteristics are shared between most triple negative and BRCA-associated breast cancers—hence the term "BRCA-ness." Since the BRCA1 gene is intimately involved in DNA repair, if you lose the ability to correct DNA damage, your cancer might become sensitive to DNA-damaging chemotherapy drugs like the platinums (Carboplatin and Cisplatin) and others like temozolomide (Temodar).

This is the theory, but is there actual evidence of platinum super-responsiveness in triple-negative breast cancer? Most of the data comes from neoadjuvant trials, where systemic treatment is offered before surgery, and then the remaining cancer in the breast and axillary lymph nodes is measured when the surgery is done afterwards. One study in neoadjuvant treatment of locally advanced early breast cancer (Stage II-III) showed an 83% pathological complete response rate (pCR) in known BRCA-carriers, meaning that in more than three quarters of the women in this very small study (n=13), no evidence of cancer could be found by the pathologist after surgery after treatment with single agent cisplatin. This supports the principle that BRCA-associated tumors are highly sensitive to this approach.

Evidence is accumulating on this question, however. In randomized trials of platinum drugs added into combination chemotherapy, pCR rates have been conflicting about the selective benefit of carboplatin. But in the CALGB 40603 trial presented at this meeting, carboplatin added to Taxol followed by dose-dense AC (Adriamycin+Cytoxan) in the neoadjuvant setting in Stage II-III breast cancer, the addition of carboplatin appeared to increase the pCR rate from 41% to 54%, although it did lead to lowered counts. This finding about the benefit of adding of carboplatin with triple-negative patients confirms the earlier GeparSixto trial. An important finding of the 40603 trial is that in the triple-negative population, Avastin, which was also tested, didn't confer any additional benefit to these patients in terms of pCR, and had significant toxicities.

In Stage IV disease it's less clear, but platinum drugs and other DNA-damaging chemotherapy like temozolomide have certainly shown promise in small series of patients with BRCA-associated cancers. It is reasonable to try this in sporadic (not-BRCA-associated) triple negative breast cancer, although it's not clear in which line of treatment carboplatin would be best.

Since there are several proven chemotherapy agents available for later lines of treatment in MBC, a key variable in selecting chemotherapy agents for treating triple negative MBC is looking at which toxicities the patient most wants to avoid. The goal is to control the disease in a way that doesn't make the patient sick. One good way to look at this is by speaking to the patient about the kinds of toxicities different chemotherapy agents have and ascertaining their preferences:

- Less hair loss: capecitabine (Xeloda), vinorelbine (Navelbine), carboplatin
- Less GI symptoms: taxanes (Taxol, Taxotere, Abraxane), gemcitabine (Gemzar)
- Less neuropathy: capecitabine (Xeloda), anthracyclines (Adriamycin, Doxil), gemcitabine (Gemzar)

- Less lowered counts: taxanes (Taxol, Taxotere, Abraxane), capecitabine (Xeloda)
- Less IVs (oral therapy): capecitabine (Xeloda)

It's important to emphasize that combination chemotherapy is only preferred for symptomatic and/or rapidly progressing tumors no matter what subtype it is, otherwise the usual approach of sequential single agent chemotherapy is preferred.

- **Antiangiogenic drug role?**

We have never had a clear strategy for the use of antiangiogenic drugs in MBC, although evidence suggests that these agents may be as good (or as lacking) as in any other subtype. All the trials show a modest month to five month increase in the time it takes for the cancer to progress (PFS) and in response rates with the addition of Avastin to chemotherapy, but no benefit at all from any of the trials in how long patients live (OS). Dr. Carey said she only highlights the response rates because when a patient is very symptomatic or with rapidly progressing visceral disease in liver or lung, the improved response rate of added Avastin may be something to consider.

Dr. Carey did not discuss Avastin toxicities, but it's worth pointing out that the toxicities, while they can be monitored and controlled, are significant enough that FDA rescinded approval based on a negative harm-to-benefit ratio.

- **How Targetable is BRCA loss?**

The BRCA1 and BRCA2 genes are involved in DNA damage and repair. The idea is that if you lose these mechanisms of repair, you will be sensitive to DNA-damaging strategies that explot DNA damage response, including: cell-cycle checkpoint conrol, DNA repair, and chromatin remodeling.

PARP inhibition is the furthest along of the different strategies, especially in BRCA-damaged cancers. Olaparib offered the first hint of efficacy but only in BRCA-associated, not sporadic, triple negative MBC. The next idea was to pair a DNA damaging agent with a PARP inhibitor, but the drug ABT-888 (veliparib) only showed responses in BRCA-associated breast and ovarian metastatic patients.

At this San Antonio meeting, a neoadjuvant study of veliparib (ABT-888) was presented from the I-SPY2 trial which is testing multiple agents so as to predict efficacy in small numbers of patients. In this study, the PARP inhibitor veliparib was tested in combination with carboplatin against a standard regimen of Taxol followed by AC. As in the other neoadjuvant trials mentioned here, the outcome was pCR, or pathological complete response, and the addition of the carboplatin+veliparib combination did increase pCR rates in patients with triple-negative Stage II-III breast cancer. It could not be ascertained how much of a role was played by the carboplatin, and how much by the veliparib, but the combination was reasonably well tolerated, with lowered counts being the primary side effect.

- **What are targets in basal-like, claudin-low, and other subsets of triple negative breast cancer?**

Other triple-negative subsets require more sophisticated approaches. In multiple datasets, 25% of triple negative tumors have "intrinsic targets" such as luminal subtypes that bring up the question of endocrine therapy or HER2-enriched subtypes, which would bring up the possibility of anti-HER2 therapies. "The jury is still out on this," said Dr. Carey.

The remainer are basal-like and claudin-low subtypes, which are very heterogenous tumors. Research is ongoing, looking at basal-like 1 and basal-like 2 (EGFR), immunomodulatory, mesenchymal, mesenchymal/stem cell and LAR (androgen receptor signaling). "Each raises the question of whether you can tease out whether DNA damage is targetable, growth factors pathways are targetable, whether immune factors are targetable, etc."

One interesting study presented at ASCO in 2012 looked at androgen-receptor positive (AR+) triple negative breast cancer targeting with a drug called bicalutamide. The idea was to find and treat an endocrine pathway in triple negative breast cancer. This study (Gucalp, ASCO 2012) showed a clinical benefit rate of 21% of stable disease for at least six months. The bad news is that you had to test 452 tumors to find the 51 that were AR+. "This is the challenge for all of us," said Dr. Carey, "As we start looking for subsets in breast cancer."

The next generation of trials will likely be "genome forward," in that they screen the whole cancer genome of patients for biomarkers, potentially matching them with specifically targeted therapies. Awareness of the heterogeneity of triple negative metastatic breast cancer is clearly the way we are going to be moving forward.