SABCS 2013: Notes from an educational session on HR+ MBC

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The goals for patients with metastatic breast cancer (MBC) are to extend survival, alleviate symptoms and improve and maintain quality of life. Frequently in HR+ (hormone responsive, which includes ER+ and/or PR+) MBC, there are clinical situations where there is non-measurable or asymptomatic, minimally measurable disease—with bone-dominant and/or pleura/abdominal metastases, small lymph nodes, and/or cutaneous lesions. The clinician's goals in addition to the above are to delay initiation of chemotherapy, offering an opportunity to practice the "art" of oncology.

You can tell the "endocrine savants" (among oncologists) because they use endocrine therapy for metastatic disease for as long as they possibly can. Clinical trials, on the other hand, often focus on response rates (tumor shrinkage) or duration of response, outcomes that aren't always aligned with disease stabilization. Many times, there will be evidence of subtle findings indicative of disease progression, but you wait and don't do anything so you can see what happens over time.

In classic studies, it has been shown that the outcomes are the same for HR+ MBC whether the patient has an overt clinical response or whether the patient has stable disease. (Robertson JFR BC Research Treatment 1999).

- **Outcomes are different for HR+ MBC than for other kinds of MBC**.

There are clear, distinctive features for HR+ MBC—subtypes tend to metastasize to different sites: HR+ MBC much more likely to go to bone, pleura and peritoneum and less likely to go to visceral sites: brain, liver and lung (Kennecke H JCO 2010;28:3271-3277). The natural history is also different, shown by data from Dana Farber data (Seah et al, JNCCN in press). These patients don't do quite as well as those with HER2+ MBC but much better than those with triple negative MBC.

Should patients get up-front endocrine therapy or chemotherapy? (Australian and New Zealand Breast Cancer Trials Group, JCO 1986:4:186-193 and Taylor SG 4th et al, Ann Intern Med 1986:104:455-461) Studies suggest that chemotherapy is no better than endocrine therapy, except for patients in "visceral crisis" or who truly need a treatment response "right now"—although responses to hormonal manipulation are sometimes rapid.

- **The original "precision/personalized/targeted'one-size-does-not-fit-all/individualized" therapy in oncology.**

Response rates in historic studies are striking. In one older study, response rates to endocrine therapy was 73% in ER+ and 7% in ER- MBC (Jensen E Cancer 1980;46:2759) It was just as "magical" as any new targeted therapy! If you look at strongly ER+ MBC tumors, you see response rates of 83% in first line HT for mets. (Osborne CK et al 1980:46:2884-8).

Today, because we use these agents as adjuvant treatment, you see lower response rates in MBC. As AIs became standard for early BC as adjuvant treatment, we increasingly look to novel endocrine agents like fulvestrant and novel pathways targeting resistance, like mTOR.

When it comes to single vs. combination endocrine therapy in premenopausal women with MBC, overall survival is better with combination GnRH agonist (buserelin) and tamoxifen. In other words, shut down ovarian function first, then use endocrine therapy—tamoxifen or an AI (aromatase inhibitor).

About sequencing, oncologists tend to use non-steroidal AI, steroidal AI and fulvestrant interchangeably.

Regarding combinations in post-menopausal HR+ MBC, two different studies in first line have conflicting results. One (FACT) shows a benefit in PFS and OS for combining anastrozole and fulvestrant; the other (SWOG 0226) does not. (Mehta NEJM 2012:367, Bergh J JCO 2012:30) The largest benefit in the positive SWOG trial appeared to be in patients who had late recurrences and hadn't received prior tamoxifen therapy. In the recent SOFEA trial, there was no difference between an aromatase inhibitor plus fulvestrant vs. fulvestrant vs. exemestane. In the SWOG trial, there was a high percentage of patients with de novo disease(39%) vs. 13% in FACT and 0% in SOFEA, and therefore a much lower proportion of adjuvant hormonal treatment on SWOG, and a greater PFS (progression free survival, the time it takes for the cancer to progress) a range of 13-15 months. So, endocrine-naive patients benefit from the combination.

An older treatment, estradiol was "revived" by Matt Ellis (Ellis JAMA 2009 302:774-780) in a small randomized study comparing 30 mg vs. 6 mg estradiol after an aromatase inhibitor (second line) for ER+ MBC, showing a clinical benefit of 29% for 6 mg dose. Clinical benefit is a measure of what percentage of patients in a clinical trial show: a complete response to treatment (known as CR, when a tumor shrinks until it can no longer found on scans), plus a partial response (known as PR, when a tumor shrinks at least 50%), plus stable disease for a minimum of 6 months (SD).

The NCCN (the National Comprehensive Cancer Network, which publishes guidelines) the list of endocrine therapies used in the treatment of MBC includes, but the first four are more potent with fewer toxicities:

- Non-steroidal aromatase inhibitor—anastrozole(Arimidex), letrozole (Femara)
- Steroidal aromatase inactivator—exemestane (Aromasin)
- Fulvestrant (Faslodex), an estrogen antagonist
- Tamoxifen or toremifene, selective estrogen receptor modifiers or SERMs
- Megestrol acetate (Megace), a progestin
- Fluoxymesterone (Halotestin), an anabolic steroid
- Ethinyl estradiol (estradiol), a form of estrogen

Note: premenopausal patients with ER+ disease should have ovarian ablation/suppression and follow postmenopausal guidelines.

- **Linking anti-estrogen treatments to other pathways.**

Crosstalk: ER and mTOR Pathways. There are potential pathways linking the ER and mTOR pathways, as well as growth factor signaling with ER and HER2, which invites "all sorts of ways" of combining anti-estrogen therapies with these signaling pathways. A successful example of this is the BOLERO-2 study comparing exemestane alone vs. exemestane + everolimus (Afinitor) in HR+ MBC that had progressed on an aromatase inhibitor. This large randomized trial showed increased response rates and longer time to progression (Baselga NEJM

2012;366: 520-529). Unfortunately, the side effects are considerable and related to target: stomatitis (mouth sores), rash, hyperglycemia and a rare but serious pneumonitis. Mitigating stomatitis by using steroid mouthwash prophylactically is being tested (Rugo, O'Shaughnessy). The TAMRAD trial looking at tamoxifen vs. tamoxifen + everolimus had similar response rates for each arm, but a longer PFS for the combination.

The TANDEM trial that combined anastrozole with trastuzumab (Herceptin) showed a modest improvement in PFS, not comparable to that with chemo + Herceptin, but there appears to be a fraction (appears to be about 20%) of patients who can use an "all biologicals" regimen, targeting the ER and HER2 receptors, and go for years on it without progression. (Kaufman JCO 2009:27:5529-5537)

Similar studies looked at letrozole with lapatinib (Tykerb), a dual kinase inhibitor that targets both the EGFR and HER2 gene, but they saw no aggregate benefit for the combination. However, for the HER2+ and ER+ patients there was a modest improvement in PFS. The CALGB 40302 study of fulvestrant with/without lapatinib for HR+ MBC after an AI had failed, showed no benefit for patients with HER2-negative cancers, but a small 6 vs. 3 months PFS for HER2+ cancers with the combination (Burstein SABCS 2010).

Recently, there has been great interest in CDK Inhibitors. The farthest along in clinical development is palbociclib (PD 0332991), a CDK4/6 inhibitor (Finn Breast Cancer Res 2009; 11). Palbociclib had substantial preclinical activity in ER+ luminal cell lines, and in randomized Phase II data presented at last SABCS 2012, they showed data for HR+ MBC that combining palbociclib with letrozole vs. letrozole alone in first line increased PFS from 7.5 months to 26.1 months. The major side effects are neutropenia and other asymptomatic marrow suppression (Finn SABCS 2012).

- **Genomic medicine will change the landscape**.

There is a broad expectation that genomic medicine will quickly change the landscape, and if you look at the specific mutations (showed a slide with a "heat map" from the Cancer Genome Atlas) you can see how investigators will be moving forward.

- **Final clinical tip**

Don't forget to go back to endocrine therapy. One of the most common suggestions we (at Dana Farber) make for patients with initially hormone sensitive MBC who have had multiple lines of chemotherapy is to revisit the endocrine therapies, even in late stage disease. "We probably don't reintroduce endocrine therapy frequently enough."

So what does the sequence of endocrine therapies look like in December 2013? For those patients who are endocrine naïve, or who've had little endocrine therapy: if they're premenopausal, in the first line, it's a combination of ovarian function suppression and tamoxifen. If they're postmenopausal, I'm intrigued by data suggesting that combination therapy works particularly well in patients who have not had prior therapy, so I look at that SWOG data and am tempted to use an aromatase inhibitor with fulvestrant. In the second line, if there has been treatment with prior tamoxifen and/or an AI, fulvestrant is indicated. In 3rd line, consider an AI + an mTOR inhibitor, and when that fails, progestins, estrogens, or move on to chemotherapy.