Optimizing chemotherapy-free survival for the ER/HER2 positive metastatic breast cancer patient

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The recent incremental advances made in the treatment of metastatic breast cancer (MBC) have elicited potential for survival extension in this treatable, yet incurable population of breast cancer patients. Clinicians have focused on targeted therapies, which aim at signaling receptors such as the human epidermal receptor (HER) superfamily, the estrogen receptor (ER), vascular endothelial growth factor (VEGF), the insulin-like growth factor receptor (IGFR), the hepatocyte growth factor receptor (cMET), PI3K, mTOR, and many others.

As a result of improved systemic adjuvant therapy and early detection methods, breast cancer mortality rates have been declining annually since 1990; in women younger than 50 there was a recorded 3.2% annual decrease and in women beyond 50 there was a 2.2% annual decline in death rates.\(^1\) The inclusion of novel agents into MBC treatment has directly resulted in patients living longer with their disease.\(^2\) Although promising, these developments are marginal and MBC is often accompanied by multiple symptoms that sacrifice the patient’s quality of life. In our view, the management of MBC is on the cusp of a paradigm shift, in which well-tolerated targeted agents will become preferential to cytotoxic chemotherapy. This would result in reduction of substantial side effects and delay of possible additional symptoms and comorbidities. In addition, signaling redundancies that are hallmarks of cancer, may be hindered by targeting multiple pathways in conjunction with other targets.

The two most prominent biological targets in breast cancer research are the ER and the HER2. A majority of breast cancer patients, especially postmenopausal women, have ER
positive (around 75%) tumors and are therefore eligible to receive hormonal therapy. The endocrine agents used in hormonal positive BC include among others, the antiestrogen tamoxifen (Tam) and various aromatase inhibitors (AI) such as anastrozole (A), letrozole (L), and exemestane (E), which impede signaling through the ER. HER2 overexpression occurs in 17% to 25% of BC cases out of which 45% to 50% are also ER-positive. The overexpression of HER2 can be targeted by monoclonal antibody, trastuzumab (T) and kinase inhibitor, lapatinib.

There is increasing evidence that the ER and HER2 pathways cross-talk and thereby synergize in tumor progression. Specifically, the ER can activate the HER2 growth factor pathway which, in turn, can post-translationally modify the ER and its coactivators, thus enhancing ER-mediated transcription of genes critical for breast cancer progression. The ER activates the HER pathway by several mechanisms that include increased expression of HER ligands, activation of HER via the non genomic actions of ER, and by releasing membrane bound HER ligands to act in an autocrine manner to activate the pathway. Overexpression of HER2 is the only mechanism of resistance to endocrine therapy for which clinical data exist. For example, patients with ER+ MBC treated with L or Tam who convert to HER2+ at the time of disease progression exhibit a shorter survival compared to those who do not convert. These data clearly imply that optimal therapy against ER+/HER2+ breast cancers is a combination of endocrine therapy and HER2 inhibitors.

There are numerous clinical studies that have analyzed the combination of targeted therapies, for example, the multicenter Phase II TAnDEM study demonstrated that the combination of T and A significantly improved PFS, clinical benefit rate (CBR), and time to tumor progression (TTP), compared to A monotherapy; the primary end point, PFS, was doubled.
in the T + A arm of this hormone / HER2-positive MBC population (4.8 months vs. 2.4 months, respectively).\textsuperscript{15} Cross-talk between pathways was also evaluated in the international Phase III, EGF30008 trial; the combination of L and lapatinib significantly increased PFS by 5.2 months, over L alone in the HER2-positive cohort.\textsuperscript{4} Similarly, a phase II study of L and T revealed a clinical benefit of 52% in their group of postmenopausal women with MBC\textsuperscript{11}. 

Clinical studies have also included gefitinib (G), an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, in combination with hormonal therapy in ER-positive MBC;\textsuperscript{16} In a phase II study by Osborne et al. of two populations with ER-positive MBC (HER2 positive in 15% of patients), patients were given G or placebo in combination with Tam.\textsuperscript{16} The median PFS for G treated patients versus placebo in the stratum 1 population was 10.9 months and 8.8 months, respectively.\textsuperscript{16} The median PFS for each of the stratum 2 subgroups was 5.7 months and 7.0 months, respectively; the difference in PFS and CBR between strata were attributed to patient population differences, specifically related to prior breast cancer therapy.\textsuperscript{16} Another phase II study compared G or placebo in combination with A in newly diagnosed hormone receptor-positive MBC.\textsuperscript{17} There was a marked increase in median PFS with the addition of G to A versus placebo (14.5 months vs. 8.2 months, respectively).\textsuperscript{17} The combinations of G and A and G and fulvestrant (F) were directly compared in a randomized phase II study; the primary endpoint, CBR, was 42% in the AG group and 38% in the FG group.\textsuperscript{18} An exploratory subset analysis was conducted on two phase II trials comparing G with placebo in combination with Tam or A.\textsuperscript{19} The post hoc analysis examined the patient subsets according to prior endocrine therapy exposure; the endocrine naïve patients in both clinical trials achieved a prolonged PFS when G was combined with A or T compared to either endocrine therapy alone.\textsuperscript{19}
The research surrounding the combination of targeted therapies has just begun to scratch the surface of possibilities; active and recruiting trials propose various combinations of estrogen receptor antagonists and anti-HER2 agents. A phase II trial has been assembled to test F and/or T in the first-line setting; overall response rates is the primary objective in this hormone/HER2-positive, postmenopausal MBC group. A different first-line phase II trial investigates bevacizumab in conjunction with either F or A, with or without T in postmenopausal, hormone receptor positive MBC (with or without HER2 overamplification).

The safety and effectiveness of the combined antibodies, T and bevacizumab, exploring the possible association between HER2 overexpression and the up-regulation of VEGF, was tested in a phase I/II study of HER2-positive MBC; the trial results are currently pending and the results are awaited. Another phase II study focusing on the VEGF provides preliminary data revealing the benefit of pazopanib and lapatinib in combination. In a randomized group of HER2-positive MBC patients, the lapatinib + pazopanib arm produced a greater response rate and resulted in reduced rates of progressive disease (and target lesions) compared to lapatinib monotherapy.

Combination targeted research has focused on ER and HER2-positive MBC, but what about the HER2-negative patients? Preclinical research using acquired endocrine resistance cell models by Leary et al. suggests that interruption of the HER2/ER crosstalk with lapatinib could potentially restore endocrine sensitivity in ER-positive/HER2-negative patients with acquired endocrine resistance. The ability of lapatinib to inhibit crosstalk between the HER2 and the ER in HER2-negative patients has been questioned by Mayer and Arteaga. It has been proposed that the ability of lapatinib to restore endocrine sensitivity in HER2-negative BC is limited to those patients who converted to HER2 positivity at the time of recurrence; the clinical data...
concerning percentage of patients with converted disease or acquired EGFR over-expression are limited. In a preclinical study of the molecular cross talk between the ER and EGFR, 3 (11%) of the tumors found in paired clinical breast cancer specimens, originally negative for HER-2, became amplified and/or overexpressed at time of ER resistance. The completed and ongoing clinical studies are analyzing the intricacies and patterns of breast tumor signaling and pathways; these trials reveal promising findings in combination target therapy, without the addition of cytotoxic chemotherapy. Therefore, it is reasonable to envision situations where chemotherapy can be considerably postponed in the metastatic setting. However, this suggested treatment option is conditional upon the patient’s potential response to these targeted agents. It is also important to recognize the limitations of these modern targeted therapies; the varying trial results are not without inconsistencies and fleeting tumor responses. The possibility of additional survival pathways operating in metastatic tumors is undeniable. Future research should continue to focus on optimizing ER and HER inhibition, but should also expand research to include downstream intermediates and the exploration of other possible pathways.

Avoiding or delaying cytotoxic therapy would not be appropriate for patients with rapidly progressing disease or for those experiencing visceral crisis. For these advanced patients, as well as for those without ER/HER2 positivity, cytotoxic chemotherapy is essential, with or without targeted agents. There are still certain ER+ tumors that would require chemotherapy based on basal-like signature and established aggressive disease. Nevertheless, evidence suggests that the role of cytotoxic agents may be minimized in certain patients with ER and/or HER2 sensitivity and good end organ function.

The recent clinical research in MBC, as well as early breast cancer, has begun to advocate the use of combination anti-HER2 and endocrine agents in place of cytotoxic.
chemotherapy.\textsuperscript{27,28} Currently, there are identifiable patient subsets for which combination of targeted agents prolong chemotherapy-free survival. The future goal is to identify all the personalized networks driving tumor cell proliferation and target these pathways simultaneously with combination treatment or other novel approaches.
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