



Personalized Therapy for Breast Cancer: How Long More to be There?

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Half a century ago, when the American Society of Clinical Oncology (ASCO) was founded in 1964, breast cancer was treated based on the Halstedian hypothesis of extensive surgery for locoregional control as well as distant metastasis prevention.¹ Over the last fifty years, the treatment approaches toward this morbid disease has transformed enormously.² This revolution is mostly the result of a greater understanding of the biology of breast cancer as well as the development of targeted therapies. Today, various molecular subtypes of breast cancer have been identified, and the respective clinical course and response to existing therapeutic regimens have been widely studied.³ Nevertheless, the great majority of patients in the world do not have access to genetic assays. Estrogen receptor (ER), progesterone receptor (PR), HER2, and Ki67 instead are routinely used for clinical-pathological classification in order to choose the appropriate regimen for neo- or adjuvant therapies.⁴

ER-targeted therapies are among the greatest therapeutic developments in the past 50 years. The key change in ASCO guidelines (2014) is extending adjuvant endocrine therapy for durations of up to 10 years rather than 5 years for hormone receptor positive breast cancer patients for risk reduction of recurrence and contralateral breast cancer.⁵ Switching from tamoxifen to aromatase inhibitor is based on menstrual status as

well as tolerance to either of the treatments. It should be kept in mind that additional information is still needed regarding the identification of predicting markers for recurrence and improved survival for this group of patients. Clinical trials such as TAILORx, and the RxPONDER, have applied Oncotype DX® genomic assays in order to identify ER-positive patients for whom endocrine therapy alone is enough.^{6,7} As mentioned earlier, genetic assays are only available for a very limited number of patients in the world, so doesn't it mean that in routine clinical practice we are yet following one-size-fits-all adjuvant endocrine therapy?

In the late 1980s, poor clinical outcome was correlated with HER2 gene amplification in early breast cancers, and in late 1990s the survival benefit of trastuzumab when added to standard chemotherapy was shown for HER2 positive metastatic breast cancers.^{8,9} This changed the clinical use of HER2 from a prognostic marker (for worse survival) to a target therapy for HER2-positive patients who account for about 15–20% of breast cancers. Resistance to trastuzumab occurs both in the adjuvant and metastatic settings and again our understanding of mechanisms for resistance are limited.

However, to overcome this resistance, clinical trials using dual HER2 blockade with other tyrosine kinase inhibitors plus trastuzumab were initiated. Although the combination of trastuzumab and lapatinib in the neoadjuvant setting (Neo ALTTO) was reported in 2012 to improve pathological complete response (pCR) rate when compared to any of the agents alone, during the 2014 ASCO annual meeting, the investigators reported that this doubling in pCR cannot translate into improved survival outcomes

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the adjuvant setting.^{10,11} ALLTO results showed that at 4.5 years median follow up, combination therapy versus trastuzumab showed small improvement in DFS, however it is not statistically significant (HR = 0.84, 97.5% CI: 0.70–1.02, P = 0.048) in addition to higher adverse effects in combination therapy group. Hormone receptor status could not modify survival rate.

In our battle against breast cancer, so far we seem to lack any specific target to attack triple-negative breast cancers that account for about 15 - 25% of breast cancers. This group includes most of BRCA1 mutated tumors and has shown to be responsive to DNA damaging chemotherapy like platinum salts, and in some studies PARP inhibitors.^{12,13} However, most of the studies are in the neoadjuvant setting where pCR is set as the endpoint, therefore further studies are necessary to analyze the impact on survival.

ASCO celebrated its 50th anniversary this year. Many believe the management of breast cancer has been transformed dramatically over the past half century from disfiguring surgery to biology-driven therapeutics. Although the morbidity and mortality of breast cancer during the last few decades is reported to be reduced, incidence rates continue to increase and we seem to have challenging hurdles to overcome before we can claim a personalized tailor-made therapy in every day clinical practice.¹⁴ In our future approaches to breast cancer care, we should not forget that a successful therapy is the one which is accessible for all who suffer from the disease; almost half of breast cancer cases and approximately 60% of deaths occur in less developed countries with very limited access to new assays and therapeutic agent¹⁵.

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