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Does Lapatinib Work against HER2-negative Breast Cancers?

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Abstract

Aberrant growth factor receptor signaling can augment or suppress estrogen receptor (ER) function in hormone-dependent breast cancer cells and lead to escape from anti-estrogen therapy. Interruption of HER2/ER cross-talk with lapatinib can restore sensitivity to anti-estrogens and thus, should be investigated in combination with endocrine therapy in patients with ER+/HER2–negative breast cancers.

In this issue of *Clinical Cancer Research*, Leary and colleagues (1) explore the role of epidermal growth factor receptor (EGFR)/HER2 inhibition in endocrine resistance and its effect on estrogen receptor (ER)-HER2 cross-talk.

Preclinical studies with breast cancer cell lines and limited clinical data suggest that estrogen receptor (ER)-positive breast cancers initially inhibited by tamoxifen or by hormone deprivation can upregulate EGFR and HER2 signaling in order to bypass ER blockade (2). This mechanism involves “crosstalk” between growth factor receptor signaling and the ER. Specifically, ligand-bound ER can activate growth factor signaling, which, in turn, can post-translationally modify the ER and its co-activators and co-repressors, thus enhancing ER-mediated transcription of genes involved in breast cancer progression (Fig. 1). In other cases, cells that adapt to estrogen deprivation overexpress active Erk, which then downregulates ER expression (3, 4), thereby reducing hormone dependence. The interdependence of these pathways is further highlighted by examples in which inhibition of HER2 with trastuzumab or the HER2/EGFR tyrosine kinase inhibitor (TKI) lapatinib (5) restores detectable ER to ER-negative tumors or upregulates ER transcription in HER2-overexpressing (HER2+) breast cancer cells, respectively. Interestingly, treatment with aromatase inhibitors or downregulation of ER with fulvestrant or RNA interference (RNAi) inhibited growth of tumors or cells that had progressed on trastuzumab or lapatinib (6, 7). These data suggest that 1) oncogene overexpression can be acquired during escape from anti-estrogens, 2) inhibition of oncogenic pathways can induce (compensatory) upregulation of ER signaling, and 3) combined inhibition of ER and oncogene signaling may provide more effective control of ER+ tumors. We should emphasize that HER2 over-expression is the only mechanism of anti-estrogen resistance with supportive clinical data. This was shown in the TANDEM trial in which anastrozole ± trastuzumab was evaluated in 207 patients with ER+/HER2+ metastatic breast cancer (MBC); median progression-free

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survival (PFS) and clinical benefit rate were significantly better in the combination arm (8). However, only a minority of ER+ breast cancers harbor *HER2* gene amplification at the time of diagnosis (9, 10), suggesting that, for the majority of these tumors, mechanisms of escape from endocrine therapy remain to be discovered.

In this issue, Leary and colleagues examined cells selected for acquired endocrine resistance (estrogen deprivation, LTED; tamoxifen, LTam). Upon selection, both LTED and LTam cells exhibited upregulation in HER2, P-HER2, P-Akt, and P-Erk. Lapatinib restored sensitivity to tamoxifen or estrogen deprivation in both cells but had no effect against parental cells prior to selection. The effects of lapatinib on ER signaling varied depending on the nature of the HER2/ER crosstalk. In LTED cells, characterized by enhanced ER function, lapatinib suppressed ER genomic activity as measured by Ser¹¹⁸ P-ER levels, ER transcriptional activity, and *PGR* expression. In contrast, in LTam cells with reduced ER activation, lapatinib reactivated ER genomic function. The authors also examined paired tissue samples from patients treated with adjuvant tamoxifen. Ten of 52 (19%) tumors that relapsed during or shortly after adjuvant tamoxifen exhibited high levels of the HER2 protein by immunohistochemistry or *HER2* gene amplification in the recurrent cancer with either suppressed or enhanced ER-PR expression (1), mirroring to some extent what had been reported in previous studies with cell lines.

The EGF30008 randomized study of letrozole ± lapatinib in 1,278 patients with postmenopausal ER+ MBC with any level of HER2 was reported recently (11). In this trial, the addition of lapatinib to letrozole resulted in a significant increase in the median PFS in the subgroup of 219 patients with HER2+ cancers. Not surprisingly, this benefit was not seen in patients with HER2–negative (HER2–) tumors as a whole. In the HER2– cohort, however, a trend toward a prolonged PFS from 3.1 versus 8.3 months favoring the combination was observed in patients who experienced relapse less than 6 months since the discontinuation of tamoxifen (hazard ratio = 0.78, P = 0.117). Interestingly, the subset of patient within this group that had the lowest quartile of ER expression was the only one that benefited from the addition of lapatinib to letrozole (13.6 versus 6.7 months; hazard ratio = 0.65, P < 0.005; ref. 12). The combination of letrozole and lapatinib was well tolerated and ~15% of patients derived prolonged benefit from both drugs with a median time of treatment of 40 weeks. Considering this outcome and the toxicity and higher cost of alternative treatment with chemotherapy, it is critically important to identify molecular biomarkers in ER+/HER2– tumors that would benefit from combined endocrine and anti-HER2 therapy.

It is in the context of this important trial that we will discuss the implications of the study by Leary and colleagues. The results in EGF30008 in the HER2– group suggested some tumors in this cohort may have converted to HER2+ at the time of recurrence and thus benefited from the combination of lapatinib and letrozole. In this study, 10 out of 52 (19%) patients with (presumably early) recurrences after or during adjuvant tamoxifen converted to HER2+ as defined by ≥ 2 copies of the HER2 gene by FISH or a 3+ HER2 score by immunohistochemistry. Clearly, for these patients, particularly those with minimal symptoms, a combined approach of anti-estrogen therapy with trastuzumab or with lapatinib is an option based on the randomized trials discussed above (8, 11). If we apply this rate of “conversion” of 19% to the 200 patients in the HER2– cohort (at diagnosis) who experienced relapse <6 months since stopping tamoxifen in EGF30008, it is difficult to explain the improvement in PFS in this subgroup as a function of the addition of lapatinib to letrozole. Therefore, we would have to invoke other acquired mechanisms of escape from tamoxifen that can be ameliorated by lapatinib. These would include overexpression of EGFR, the other target of lapatinib, and ligand-induced hyperactivation of HER2 and/or EGFR signaling in the absence of receptor overexpression. Unfortunately, these possibilities were not part of the reported molecular profiling applied to the tumor relapses. An unbiased

profiling using state-of-the-art molecular methods is sorely needed in patients with ER+ tumors at the time of recurrence. If just examining one biomarker, in this case HER2, showed a 19% discordance between the diagnostic and recurrent tumor, we can anticipate many other discordant (or acquired) molecular alterations potentially causal to the escape from hormone dependence. This is also important for the rational development of many molecular therapeutics that are ready to be tested in combination with anti-estrogens in ER+ tumors with high odds of an early recurrence.

So, based on the article by Leary and colleagues, is lapatinib worth investigating in ER+/HER2- tumors? Yes. Is it likely to be effective in ER+/HER2- tumors? Not really, unless they have converted to HER2+ or acquired EGFR over-expression or ligand-(hyper)activated single copy HER2 or EGFR. Is there a “biomarker” that can prospectively select those patients with ER+/HER2- tumors that will convert to cancers that become HER2 (or EGFR)-dependent and, therefore, benefit from the addition of lapatinib to endocrine therapy upfront? Not yet but low ER might be one within a panel of biomarkers that identifies such patients. In the absence of such selectable biomarker, early progression after adjuvant endocrine therapy or first-line endocrine therapy in the metastatic setting should remain as the only criteria for selection into prospective trials. We fully agree with Leary and colleagues that treatment strategies should be based on the phenotype of the tumor at relapse rather than at diagnosis. Until we redefine the molecular profile of all ER+ cancers at the time of early or late recurrence to identify those potential pathogenic mechanisms of resistance to anti-estrogens, we may have to continue to “shoot in the dark.” In the meantime, new drugs targeting potential mechanisms of anti-estrogen resistance in patients with ER+/HER2- MBC should be added to endocrine therapy after progression on this therapy but not before progression.

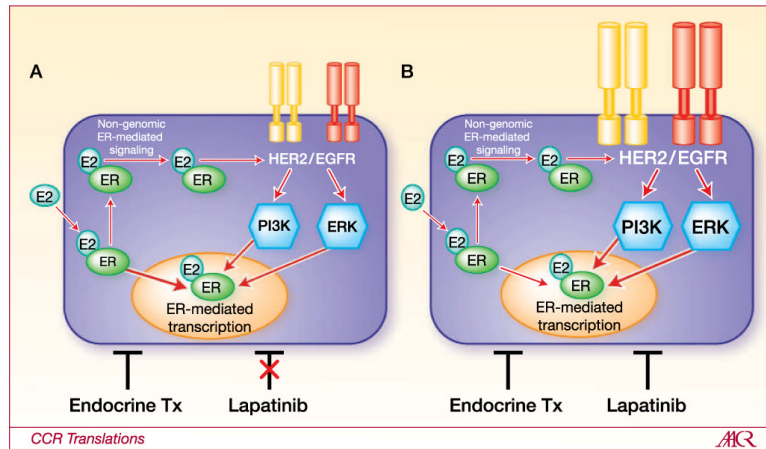
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**Fig. 1.**

A, in hormone-dependent ER+ breast cancer cells, estrogen (E2) activates ER-mediated transcription (genomic pathway) and nongenomic ER-mediated signaling. Under these conditions, the crosstalk from growth factor receptor signaling (i.e., HER2/EGFR) to ER-mediated transcription is not prominent, hence lapatinib does not exert a growth inhibitory effect. B, upon acquisition of tamoxifen resistance or adaptation to hormone deprivation, HER2 and/or EGFR signaling to PI3K and ERK becomes amplified. These pathways, in turn, enhance ER-mediated transcription by post-translationally modifying the ER and its co-activators and co-repressors. In some cases (not illustrated here) amplification of these oncogenic signals results in ER downregulation and promotes hormone independence. In the study of Leary et al. discussed herein both MCF-7 cells that adapted to hormone deprivation, the equivalent to treatment with an aromatase inhibitor, and those that became resistant to tamoxifen were sensitive to lapatinib as long as estrogen was absent or tamoxifen was given concomitantly. In contrast, lapatinib was inactive against the hormone-dependent parental cells prior to selection. If we accept the MCF-7 model as one that is representative of the majority of ER+ hormone-dependent breast cancers, we would have to assume that lapatinib is only worth adding at the time of escape from primary endocrine therapy (as in B) and not early (as in A).