Editorial

Abundant options to avoid toxicity and alternative strategies for human epidermal growth factor receptor 2-positive and hormone receptor-positive advanced breast cancer

Kazuhiro Araki, Yasuo Miyoshi

Department of Surgery, Division of Breast and Endocrine, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan

Correspondence to: Kazuhiro Araki, MD, PhD. Associate Professor, Department of Surgery, Division of Breast and Endocrine, Hyogo College of Medicine, 1-1 Mukogawa, Nishinomiya, Hyogo 663-8501, Japan. Email: ka-araki@hyo-med.ac.jp.

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Clinical oncology has progressed in elucidating multiple aspects for cancer chemotherapy. For most malignancies, we now face many therapeutic options to discuss with patients with cancer. Optimal chemotherapy-sparing regimens are preferable for patients with breast cancer. As reported in an issue of the *Journal of Clinical Oncology*, in the phase 3 ALTERNATIVE trial, 355 postmenopausal women with human epidermal growth factor receptor 2 (HER2)-positive, hormone receptor-positive advanced breast cancer who had previously received endocrine therapy and trastuzumab-containing chemotherapy were enrolled to evaluate the efficacy and safety of dual HER2-targeted therapy, including lapatinib and trastuzumab, plus aromatase inhibitors (AIs) (1). Two-thirds of the patients received a prior trastuzumab-containing chemotherapy regimen as peri-adjuvant therapy and the remaining one-third received advanced breast cancer treatment with or without prior trastuzumab as peri-adjuvant breast cancer treatment (1). Prior endocrine therapies included tamoxifen (55%), anastrozole (29%), letrozole (28%), and exemestane (8%) (1). As the first-line metastatic setting, 68% of patients were treated using lapatinib plus trastuzumab plus AIs, 57% of patients were treated using trastuzumab plus AIs, and 65% of patients were treated using lapatinib plus AIs (1). As the second-line regimen or later, 32% of patients were treated using lapatinib plus trastuzumab plus AIs, 41% of patients were treated using trastuzumab plus AIs, and 35% of patients were treated using lapatinib plus AIs (1). The most frequently administered AI was exemestane (47%) in the study, followed by letrozole (42%) and anastrozole (11%) (1). Previous treatments in the advanced breast cancer setting involved fulvestrant (n=2), pertuzumab (n=17), and trastuzumab emtansine (T-DM1) (n=1) (1). The prevalence of visceral metastases was around 20% among the three treatment arms [lapatinib plus trastuzumab plus AIs, 29 (24%); trastuzumab plus AIs, 26 (22%); lapatinib plus AIs, 18 (15%)] (1). Patients were randomized to treatments using lapatinib plus trastuzumab plus AIs (n=120), trastuzumab plus AIs (n=117), or lapatinib plus AIs (n=118) (1).

The primary endpoint was statistically improved, as follows: the median progression-free survival (PFS) was 11 months (95% CI, 8.3–13.8) in patients who received lapatinib plus trastuzumab plus AIs versus 5.7 months (95% CI, 5.5–8.4) in those who received trastuzumab plus AIs [hazard ratio (HR) 0.62 (95% CI, 0.45–0.88); P=0.0064] (1). The median PFS in patients who received lapatinib plus AIs was 8.3 months (95% CI, 5.8–11.2; HR 0.71; 95% CI, 0.51–0.98; P=0.0361, compared with those who received trastuzumab plus AIs) (1). This study indicated that the triplet therapy of lapatinib plus trastuzumab plus AIs showed a relevant clinical benefit in PFS compared with that shown by trastuzumab plus AIs, indicating a statistically

significant reduction in the risk of disease progression (HR 0.62) (1). Therefore, we believe that the triplet therapy regimen is a more desirable option than single HER2-targeted therapy in combination with endocrine therapy.

The safety reports of the three treatment arms were consistent with the previously known information of all the treatment drugs (1). The most common adverse events (any grade, and ≥10% in any arm) were as follows: diarrhea, 69% with lapatinib plus trastuzumab plus AIs, 9% with trastuzumab plus AIs, and 51% with lapatinib plus AIs; rash, 36% with lapatinib plus trastuzumab plus AIs, 2% with trastuzumab plus AIs, and 28% with lapatinib plus AIs; nausea, 22% with lapatinib plus trastuzumab plus AIs, 9% with trastuzumab plus AIs, and 22% with lapatinib plus AIs; and paronychia, 30% with lapatinib plus trastuzumab plus AIs, 0% with trastuzumab plus AIs, and 15% with lapatinib plus AIs (1). Any adverse events were usually less severe than grade 3 (1). Although adverse events were more frequent in the treatment arms including lapatinib, the incidence of treatment termination was low among those patients, and it was lower with lapatinib plus trastuzumab plus AIs (3%; n=4), than with trastuzumab plus AIs (6%; n=7) and lapatinib plus AIs (9%; n=11) (1). Based on these results, the authors mentioned that lapatinib plus trastuzumab plus AIs was well tolerated and a few patients were withdrawn from triplet therapy than those in the other doublet groups (1).

It remains unclear which patients would be suitable for chemotherapy or endocrine therapy among those with HER2-positive and estrogen receptor (ER)-positive/progesterone receptor (PgR)-positive or -negative advanced breast cancer. In these circumstances, for patients who have contraindications of chemotherapy, or for those who wish to avoid chemotherapy toxicity, endocrine therapy would be a reasonable option (2,3). On the other hand, HER2-targeted therapy combined with chemotherapy indicated improvements in survival benefits and is a favorable strategy for most first-line treatments (4). Chemotherapy in combination with HER2-targeted therapy is indicated in *de novo* and visceral-dominant disease, because this treatment offers a survival benefit compared with that of chemotherapy alone (5). A recent tissue-based biomarker study attempted to evaluate the significance of trastuzumab efficacy for patients with HER2- and ER-positive breast cancer in the HERceptin adjuvant (HERA) trial, and then, showed that expression patterns of both HER2 and ER affected the benefits of trastuzumab (6). Trastuzumab efficacy was found in both ER-positive and -negative breast cancer; HER2 expression patterns were also found using immunohistochemical analysis and HER2 fluorescence in situ hybridization (FISH) levels, except in those with a low ER-positive/HER2 FISH ratio (≥2 to <5) [disease-free survival (DFS): intention-to-treat (ITT) 0.89 (95% CI, 0.65–1.21), P value for interaction =0.07; overall survival (OS): ITT 1.27 (95% CI, 0.81–2.01), P value for interaction =0.007] (6). Consistent with immunohistochemical analysis, exploratory analyses of the estrogen receptor 1 (*ESR1*) gene expression levels for both endpoints were also observed (P values for interaction: DFS =0.06; OS =0.02), indicating that breast cancers with higher *ESR1* gene expression levels also obtained less benefit from trastuzumab (6). Therefore, low expression patterns of the HER2 protein or low *HER2* gene amplification were associated with reduced efficacy and shorter duration of response for trastuzumab (6), as crosstalk pathways between HER2 and ER signaling had been evaluated in preclinical models (7). Therefore, predominant ER signaling pathways could reduce the efficacy of HER2-targeted therapy in HER2- and ER-positive breast cancer, even in clinical settings. For that reason, in cases of predominant ER signaling, we might apply endocrine therapy in combination with HER2-targeted therapy.

Furthermore, in patients with ER- and HER2-positive advanced breast cancer, multiple previous studies have demonstrated that the addition of single HER2-targeted therapy to endocrine therapy improved PFS without a demonstrated improvement in OS than those of endocrine therapy alone in first-line settings (8-10). Previous studies have evaluated the addition of HER2-targeted therapy to AIs in postmenopausal women in the first-line metastatic setting (8). In the TAnDEM study, 207 patients were randomized to receive anastrozole (1 mg daily) plus trastuzumab (4 mg/kg loading dose, followed by 2 mg/kg weekly) or anastrozole alone (8). The combination arm revealed statistically significant benefits in PFS (4.8 *vs.* 2.4 months; HR 0.63), but did not indicate a statistical improvement in OS (28.5 *vs.* 24 months) (8). The response rate was also favorable in the combination arm (20% *vs.* 7%) (8). The most common toxicities observed in the combination arm were vomiting (21%), fatigue (21%), and diarrhea (20%); however, the most frequent toxicities were grades 1 and 2 (8).

Along the same line, in the eLEcTRA study, trastuzumab in combination with letrozole was compared with letrozole alone (9); 57 postmenopausal women were randomized to receive letrozole (2.5 mg daily) with or without trastuzumab (4 mg/kg loading dose, followed by 2 mg/kg weekly) (9).

Furthermore, patients with HER2-negative breast cancer were registered as a third cohort and were treated with letrozole alone (9). This study faced slow accrual and had early interruption before the designated 370 cases were registered (9). However, trastuzumab in combination with letrozole showed significant benefits in the time to progression (14 *vs.* 3 months; HR 0.67), the duration of which was parallel to the duration achieved in the HER2-negative group (15 months) (9). Both the response and clinical benefit rates were 27% *vs.* 13% and 65% *vs.* 39%, respectively, in favorable benefit for trastuzumab plus letrozole (9).

Furthermore, a third study (EGF30008) compared lapatinib (1,500 mg daily) in combination with letrozole (2.5 mg daily) to letrozole alone (10). In total, 219 of 1286 patients were eligible who had ER- and/or PgR- and HER2-positive invasive breast cancer (10). In that subgroup, lapatinib in combination with letrozole conferred statistically significant PFS (8 *vs.* 3 months; HR 0.71) and response rate (28% *vs.* 15%) (10). OS was not significantly different (33 *vs.* 32 months) (10). Similar to previous results in patients treated with lapatinib, diarrhea was significantly more common in the combination arm (grade 3 and 4 diarrhea: 10% *vs.* 1%) (10).

These three studies should also enhance the continuation of clinical research in the field of combined endocrine and HER2-targeted therapies (8-10). Recent evidence on multiple HER2-targeted therapies suggests the clinical benefits of dual HER2-targeted therapies for HER2-positive breast cancer (3). The most recent study, PERTAIN, was a randomized phase II trial to explore treatment using AIs in combination with trastuzumab plus pertuzumab compared to AIs plus trastuzumab in patients with first-line hormone receptor-positive/HER2-positive postmenopausal advanced breast cancer (NCT01491737) (11). This study enrolled 258 patients who were not previously treated with systemic endocrine therapy for advanced breast cancer. Patients received trastuzumab (with or without a taxane for 18–24 weeks) plus an AI (anastrozole or letrozole), or trastuzumab (with or without a taxane for 18–24 weeks) plus pertuzumab and an AI (11). Patients in the pertuzumab arm exhibited a median PFS of 18.9 months, compared to 15.8 months in those who received trastuzumab plus an AI (HR 0.65, P=0.0070) (11). The pertuzumab arm revealed favorable outcomes across all subgroups, irrespective of previous induction chemotherapy (11). The overall response rate in the ITT population was not significantly different: 63.3% for patients in the pertuzumab arm (7.3% complete responses), compared to 55.7% (0.9% complete responses) in those in the control arm (P=0.2537) (11). Nevertheless, the duration of responses was statistically significant in the pertuzumab arm: 27.1 *vs.* 15.1 months (HR 0.57, P=0.0181) (11).

In this context, according to the above-mentioned several results, HER2-targeted therapy in combination with endocrine therapy would be a favorable option in first-line settings for hormone receptor-positive and HER2-positive postmenopausal advanced breast cancer. However, in reference to the ALTERNATIVE study, one-third of patients underwent multiple prior chemotherapies (1), and we must still understand how to implement lapatinib plus trastuzumab plus endocrine therapy for patients who have HER2-positive and hormone receptor-positive breast cancer, and who were already treated with chemotherapy, endocrine therapy, and HER2-targeted therapy. Because of lapatinib's toxic adverse event profile, we believe that lapatinib plus trastuzumab plus AIs might be an appreciable option beyond resistance in pertuzumab-treated patients. Furthermore, despite the absence of randomized clinical trials comparing endocrine therapy and chemotherapy, ongoing trials with a direct comparison of chemotherapy plus HER2-targeted therapy versus endocrine therapy plus HER2-targeted therapy are currently conducted in the DETECT V/CHEVENDO (NCT02344472) and SYSUCC-002 (NCT01950182) studies (12). For example, the DETECT V/CHEVENDO is a randomized phase III study that aims to compare the combination of trastuzumab, pertuzumab, and a chemotherapy (docetaxel, paclitaxel, capecitabine, or vinorelbine) with the combination of trastuzumab, pertuzumab, and endocrine therapy (tamoxifen, fulvestrant, letrozole, or anastrozole) (12). Meanwhile, we await further additional evidence.

Generally, we may believe that elderly patients would be more affected by chemotherapy-induced toxicity than younger patients. According to the CLEOPATRA ad-hoc study, 127 patients were 65 years of age or older (placebo arm: 67, pertuzumab arm: 60) (13). Patients in both younger and older age groups experienced PFS benefits with pertuzumab treatment (<65 years, HR 0.65; 95% CI, 0.53–0.80; ≥65 years, HR 0.52; 95% CI, 0.31–0.86) (13). Adverse event profiles, including diarrhea, fatigue, asthenia, decreased appetite, vomiting, and dysgeusia, were reported more frequently in patients 65 years of age or older than in younger patients (13). Thinking about chemotherapy-sparing regimens, patients who have low tumor burden, duration of long disease-free period, and indolent disease phenotype, and also significant comorbidities, would be

suitable candidates in whom to avoid additional toxicity when treated with endocrine therapy rather than toxic chemotherapy (14). Consistent with the Cancer Treatment and Survivorship Statistics in 2016, 75% of breast cancer survivors were elderly individuals aged older than 59 years (15). Elderly patients with cancer are frequently under-treated, are a minority population in clinical trials, and have poorer survival than younger patients (16). Chronological age must be a poor predictive factor of cancer treatment-induced tolerability and the heterogeneity of elderly patients requires a cautiously personalized strategy to treat based on individual frailty (16). More than 50% of elderly patients with cancer exhibit frailty (16). These patients also exhibit an increased risk of chemotherapy-related intolerance and mortality (16). Nevertheless, the optimal evaluation to guide treatment decisions for elderly patients with cancer is still not elucidated (17). In general oncology practice, we can apply performance status to manage elderly patients with cancer, albeit standard geriatric medicine handles comprehensive geriatric assessment (17). A recent comprehensive geriatric assessment study showed that treatment-related tolerability and clinical outcomes, irrespective of functionally normal performance status, could be affected in elderly patients with cancer (17). Because elderly patients with cancer who had normal performance status had multiple comorbidities and polypharmacy based on this study, we might carefully choose not only chemotherapy, but also endocrine therapy, even in elderly patients with HER2- and ER-positive advanced breast cancer (17).

There is no single optimal strategy and choice of treatment established for patients with advanced, heavily treated breast cancer, because they might have multiple factors: not only prior therapy, toxicity, general organ functional status, and comorbidities, but also patient preference (18). A previous Japanese questionnaire-based study indicated that women with breast cancer tend to prefer endocrine therapy to chemotherapy in cases with the same treatment benefits (19). Therefore, endocrine therapy in combination with HER2-targeted therapy might be a preferable option for patients with HER2- and ER-positive, advanced, heavily treated breast cancer.

In conclusion, the PFS benefits obtained using lapatinib plus trastuzumab plus AIs in patients with HER2- and ER-positive advanced breast cancer who had been previously treated with trastuzumab and endocrine therapy are clinically meaningful and robust. The ALTERNATIVE trial showed relevant clinical benefits with a relatively good tolerability, supporting that patients with HER2- and ER-positive advanced breast cancer who are not candidates for cytotoxic chemotherapy can be adequately treated with dual HER2 blockade (lapatinib plus trastuzumab) plus AIs. This combination can potentially offer an effective and well-tolerated, chemotherapy-sparing alternative treatment regimen for patients in whom chemotherapy is not intended. Although combined chemotherapy and HER2-targeted therapy remains the treatment of choice currently, the combination of HER2-targeted therapy and endocrine therapy is a valid option that expands the available choices for this patient population and should be considered in individualized clinical settings. Furthermore, it is anticipated that HER2-targeted therapy and endocrine therapy could eliminate or reduce the need for cytotoxic-based therapy in this patient population.

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Footnote

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