



Tailor the adjuvant hormonal manipulation for premenopausal breast cancer patients

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Comment on: Coombes RC, Kilburn LS, Tubiana-Mathieu N, *et al.* Epirubicin dose and sequential hormonal therapy-Mature results of the HMFEC randomised phase III trial in premenopausal patients with node positive early breast cancer. *Eur J Cancer* 2016;60:146-53.

Submitted Jul 20, 2016. Accepted for publication Jul 27, 2016.

doi: 10.21037/tcr.2016.08.27

View this article at: <http://dx.doi.org/10.21037/tcr.2016.08.27>

The 2016 publication titled “The hormonal manipulation 5-Fluoro-uracil Epirubicin Cyclophosphamide (HMFEC) trial” in the *European Journal of Cancer* provided an opportunity to revisit the adjuvant HM of premenopausal breast cancer (BC) patients (1). In the HMFEC study, premenopausal BC patients with positive lymph node involvement were randomized in a 2×2 factorial fashion to groups either administered FE50C *vs.* FE75C followed by HM or no HM. Gonadotrophin-releasing hormone agonists (GnRH_a) were used for HM if patients retained menstrual cycle after chemotherapy; for patients became amenorrhea after chemotherapy, tamoxifen was administered. As expected, HM benefit was not seen in ER-negative population. In the ER-positive/ER-unknown subpopulation, the HM provided modest and nonsignificant recurrence reduction [hazard ratio (HR) 0.85, 95% confidence interval (CI) 0.62–1.17, P=0.32] (1). The authors justified the unexpected results in ER-positive premenopausal BC patients by citing inadequate power and small event number. In addition, the HM used in this trial is generally considered an inadequate adjuvant endocrine therapy for premenopausal BC patients. Nevertheless, HMFEC was designed 30 years ago to tackle an important question of whether HM is beneficial for premenopausal BC patients who had received chemotherapy, at a time that the 1998 Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) meta-analysis has shown that adding either tamoxifen or ovarian ablation to chemotherapy in premenopausal patient did not improve patient outcome (2).

Thirty-years later, with mounting evidences, the 2016 American Society of Clinical Oncology (ASCO) guideline now suggests that tamoxifen +/- ovarian suppression, or ovarian suppression + aromatase inhibitor (AI) to be a treatment of choice for premenopausal BC patients (3). The findings of the HMFEC trial and the paradigm shift in the guideline from 1998 to 2016 provide an opportunity to examine the history and optimization of the adjuvant endocrine treatment for ER-positive premenopausal BC patients.

Efficacy of adjuvant ovarian ablation or suppression

In the 1996 EBCTCG meta-analysis, ovarian ablation with oophorectomy, radiation, or GnRH_a was shown to reduce BC recurrence and death in patients aged younger than 50 years, but only reached statistical significance in the chemotherapy-absent subgroup (4). In the follow-up 2005 EBCTCG meta-analysis, it revealed similar but significant risk reduction of BC recurrence and mortality by ovarian ablation or suppression in patients under the age of 50, but with a more modest effect for those who had received chemotherapy as part of the adjuvant treatment (5). In contrast, in the 2007 meta-analysis by the LHRH-agonists in Early Breast Cancer Overview Group, the addition of a LHRH agonist with or without tamoxifen after chemotherapy significantly reduced the risk of recurrence or death, especially in patients under the age of 40, a

Table 1 Summaries of studies investigating the effect of GnRHa only or in addition to tamoxifen or aromatase inhibitor as adjuvant hormonal therapy in breast cancer

Trial	No. of patients	Treatment	DFS rate [years]	HR for DFS	OS rate [years]	HR for OS
HMFE (ER+/ER unknown subgroup)	443	FEC + GnRHa or tamoxifen vs. FEC + no treatment	NR	0.85 (0.62–1.17)	NR	1.40 (0.88–1.23)
EBCTCG 2005	7,725	OFS vs. no treatment	52.7 [15]; 48.4 [15]	0.83 (0.79–0.87)**	59.7 [15]; 56.5 [15]	0.87 (0.82–0.92)**
LHRH agonist Early Breast Cancer Overview Group	2,671	GnRHa plus chemotherapy +/- tamoxifen vs. chemotherapy +/- tamoxifen	NR; NR	0.88 (0.77–0.99)**	NR; NR	0.85 (0.73–0.99)**
ABCSG-12	1,803	OFS + anastrozole vs. OFS + tamoxifen	92.0 [5]; 92.8 [5]	1.13 (0.88–1.45)	94.1 [8]; 96.3 [8]	1.63 (1.05–2.52)*
SOFT (chemotherapy subgroup)	1,084	OFS + tamoxifen vs. tamoxifen	80.7 [5]; 77.7 [5]	0.82 (0.64–1.07)	94.5 [5]; 90.9 [5]	0.64 (0.42–0.96)*
SOFT and TEXT combined analysis	4,690	OFS + exemestane vs. OFS + tamoxifen	92.8 [5]; 88.8 [5]	0.72 (0.60–0.85)**	91.1; 87.3	1.14 (0.86–1.51)

*, P<0.05; **, P<0.01. ABCSG, Austrian Breast and Colorectal Cancer Study Group; DFS, disease free survival; EBCTCG, Early Breast Cancer Trialists' Group; HMFE, Hormone manipulation 5FU Epirubicin Cyclophosphamide study; HR, hazard ratio; GnRHa, Gonadotropin-releasing hormone agonist; NR, not reported; OFS, ovarian function suppression; OS, overall survival; SOFT, Suppression of Ovarian Function Trial; TEXT, Tamoxifen and Exemestane Trial.

group who were less likely to become amenorrheic after chemotherapy (6). This was the first signal suggesting that addition of ovarian suppression maybe beneficial for those who remained premenopausal after adjuvant chemotherapy. In the Suppression of Ovarian Function Trial (SOFT), ovarian suppression plus tamoxifen did not show significant improvement in disease-free survival (DFS) and overall survival (OS) as compared with tamoxifen only in the overall study population of premenopausal BC patients; however, when the analysis was limited to those who had a higher risk of recurrence thus to receive either neoadjuvant or adjuvant chemotherapy, the effect on DFS and OS was more pronounced and significant (*Table 1*) (7). Based on the updated results, current ASCO guideline recommends tamoxifen plus or minus ovarian suppression as the choice of adjuvant hormonal therapy for premenopausal BC patients.

Comparison between tamoxifen and AI with the use of ovarian ablation or suppression: conflicting data

For postmenopausal BC patients, AI is generally considered more advantageous than tamoxifen in terms of both BC

control and OS (8). Whether this statement holds true in the premenopausal setting remains to be determined. In the phase III neoadjuvant clinical trial (STAGE) comparing goserelin plus either anastrozole or tamoxifen in premenopausal BC women in Japan, the anastrozole arm had a significantly higher tumor response rate as compared with tamoxifen (70.4% vs. 50.5%, P=0.004), suggesting a higher anti-tumor efficacy of AI as compared with tamoxifen in premenopausal patients receiving GnRHa (9). However, in Austrian Breast and Colorectal Cancer Study Group 12 (ABCSG12) study, where premenopausal women were randomized to either goserelin plus anastrozole or goserelin plus tamoxifen, there was no significant difference in terms of DFS at the first 5 years (HR 1.10; 95% CI, 0.78–1.53; P=0.59) (10). After a median of 8 years of follow-up, the final analysis of OS showed that the anastrozole arm had a significant worse survival as compared with the tamoxifen arm (HR 1.63; 95% CI, 1.0–1.45; P=0.03) (11). There are various explanations for this unexpected result (discussed later) but this also further complicates the choice of hormonal agent along with GnRHa as adjuvant hormonal therapy for premenopausal women. The recent joint analysis of the SOFT and Tamoxifen and Exemestane Trial (TEXT) demonstrated different results as compared

to ABCSG12. Ovarian suppression plus exemestane had a significant DFS benefit (HR 0.72; 95% CI, 0.60–0.85; $P < 0.001$) as compared with ovarian suppression plus tamoxifen. Other endpoints such as rate of freedom from BC or distant metastasis showed similar trend, but the OS were not different between the two arms (HR 1.14; 95% CI, 0.86–1.51; $P = 0.37$) (12). The benefit of exemestane on DFS was also more profound in those who received chemotherapy. Based on these results, current ASCO guideline suggests that for premenopausal BC patients with a higher risk of recurrence, a GnRHa should be added to either tamoxifen or AI (3).

Reasons for the conflicting results of STAGE, ABCSG12 trial and SOFT/TEXT joint analysis

Two major reasons have been proposed to explain the poor survival of the anastrozole arm in the ABCSG12 trial. First, a high body mass index (BMI) may reduce the efficacy of AI. Patients with a higher BMI tend to have a higher proportion of fat, which leads to increased aromatase production; therefore, the flat dose of anastrozole may have been insufficient to achieve complete estrogen suppression. The secondary analysis of ABCSG12 showed that patients who were overweight ($BMI \geq 25 \text{ kg/m}^2$) had a nearly 50% increase in the risk of disease recurrence (HR 1.49; 95% CI, 0.93–2.38; $P = 0.08$) and a three-fold increase in the risk of death (HR 3.03; 95% CI, 1.35–6.82; $P = 0.004$) compared with tamoxifen-treated patients (13). The BMI of Asian patients is generally lower than that of Caucasian patients; this may partly explain the conflicting results of the neoadjuvant STAGE and adjuvant ABCSG12 trials.

Second, AI could stimulate ovarian estrogen production through the rebound of follicle-stimulating hormone (FSH) by stimulating the hypothalamus-pituitary pathway (14). Dowsett *et al.* recently cautioned that the plasma estradiol (E2) levels can increase in some individuals after the first month of GnRHa plus exemestane, though the mean level of E2 is lower than that after GnRHa plus tamoxifen administration (15). In the SOFT trial, 25% of the patients were found to have incomplete estrogen suppression [plasma E2 level $\geq 2.72 \text{ pg/mL}$ detected by gas chromatography tandem mass spectrometry (GC/MS/MS) assay] at least once in the first year of triptorelin plus exemestane treatment. Baseline factors associated with an on-treatment E2 level $\geq 2.72 \text{ pg/mL}$ (10 pmol/L) included no prior chemotherapy, higher BMI, and lower FSH and luteinizing hormone (LH) level (16). The proportion of patients

receiving chemotherapy may also explain the conflicting results of the clinical trials. Adjuvant chemotherapy was not allowed in the ABCSG12 and only 5–6% of the patients received neoadjuvant chemotherapy (10). By contrast, 57.4% of the patients in the SOFT/TEXT joint analysis received chemotherapy (12). Although all patients in SOFT/TEXT remained premenopausal at the time entering the study, chemotherapy has been shown to induce premature ovarian failure, which decreases the risk of incomplete ovarian suppression (17).

However, despite evidences suggested that AI may be superior in terms of BC recurrence control as compared with tamoxifen in premenopausal BC patients receiving GnRHa, AI was not superior to tamoxifen in terms of OS in both ABCSG12 and the SOFT/TEXT combined analysis (11,12). The morbidities associated with long-term metabolic and osteoporosis side effects of AIs should be taken into account when determine the choice of hormonal agent for premenopausal BC patients receiving GnRHa (18).

Current recommendations for tailoring adjuvant endocrine therapy for premenopausal BC patients

To optimize the adjuvant endocrine therapy, physicians must estimate its absolute benefit of recurrence and mortality reduction. The ASCO 2016 guideline recommends that higher-risk patients should receive ovarian suppression in addition to adjuvant endocrine therapy, whereas lower-risk patients should not; ovarian suppression may be administered with either tamoxifen or AI (3).

Although the clinical significance of incomplete ovarian suppression by GnRHa remains uncertain, many researchers have suggested that regular biochemical testing of estrogen should be seriously considered for premenopausal patients receiving GnRHa in addition to an AI as an adjuvant endocrine treatment (15,19). For example, Papakonstantinou *et al.* proposed an algorithm recommending GnRHa plus AI for 5 years in high-risk patients and/or aged ≤ 35 years who have received chemotherapy, and monitor the E2, FSH, and LH levels every 3–6 months during the period. If adequate ovarian suppression cannot be achieved, alternative treatment possibilities including switching to tamoxifen plus ovarian suppression with GnRHa for at least 5 years or bilateral oophorectomy plus AI should be sought (19).

In the real-world practice, plasma E2 level may not be measured through GC/MS/MS assay in most hospitals. For patients who did not receive adjuvant chemotherapy, the

use of tamoxifen with or without GnRHa is recommended. For patients who received adjuvant chemotherapy, ovarian suppression is recommended, but the choices between tamoxifen and AI remains controversial. Although AI seems to be more efficacious in preventing BC recurrence, this is counterbalanced by the lack of differences in OS between GnRHa plus AI group *vs.* GnRHa plus tamoxifen group and the trade-off of possibly increased risk of adverse events of AI and incomplete ovarian suppression. Physicians should thoroughly discuss the pros and cons of adjuvant HM to premenopausal BC patients to reach a tailored therapy.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor San-Gang Wu (Department of Radiation Oncology, Xiamen Cancer Center, the First affiliated Hospital of Xiamen University, Xiamen, China).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2016.08.27>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Chen TW, Lin CH, Lu YS. Tailor the adjuvant hormonal manipulation for premenopausal breast cancer patients. *Transl Cancer Res* 2016;5(S3):S380-S384. doi: 10.21037/tcr.2016.08.27