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Controversies in oncology: which adjuvant endocrine therapy is to be given to premenopausal patients with hormone receptor-positive breast cancer?

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Although young women with newly diagnosed breast cancer are at increased risk of developing more aggressive tumour subtypes as compared with older patients, most of them are diagnosed with hormone receptor-positive (ie, luminal-like) disease.[1] Hence, the majority of premenopausal women with early stage breast cancer are candidates to receive adjuvant endocrine therapy. Young age is considered a risk factor for breast cancer recurrence and death, particularly in women with luminal-like breast cancer.[2] Hence, the choice of the most appropriate adjuvant endocrine therapy is of crucial importance particularly in premenopausal patients.

For more than two decades, tamoxifen alone has been considered the standard of care as adjuvant endocrine therapy for all premenopausal patients with hormone receptor-positive breast cancer.[3 4] Nevertheless, in the last few years, the adjuvant endocrine treatment landscape of premenopausal patients with breast cancer has dramatically changed and the choice of the best approach to be used in this setting has become particularly complex. In fact, important new data on the role of ovarian function suppression (OFS) in addition to tamoxifen or its possible combination with an aromatase inhibitor (AI) have recently become available and should now be discussed with all premenopausal women candidates to receive adjuvant endocrine therapy.[5]

Two studies (the E-3193, INT-0142[6] trials and the Suppression of Ovarian Function Trial (SOFT)[7 8]) provided evidence on the role of OFS in addition to tamoxifen in these patients. In the E-3193, INT-0142 trial, 345 premenopausal women at low clinical risk of recurrence (use of chemotherapy was not allowed) were randomised to receive tamoxifen alone or tamoxifen plus OFS for 5 years.[6] The SOFT randomly assigned 3066 premenopausal women to receive 5 years of tamoxifen alone, tamoxifen plus OFS or the AI exemestane plus OFS.[7 8] In the primary analysis of the SOFT testing the benefit of adding OFS to tamoxifen, 2033 patients were included of whom 53% received chemotherapy before randomisation due to higher clinical risk of recurrence (importantly, patients with prior exposure to cytotoxic therapy could be enrolled within 8 months after chemotherapy completion only if premenopausal status was confirmed). Taken together, the results from these two trials have suggested that the addition of OFS to tamoxifen does not provide any benefit in women at low clinical risk of recurrence for whom tamoxifen alone should be still considered standard of care.[9–11] On the contrary, the addition of OFS to tamoxifen showed to significantly improve the outcomes of women considered at higher clinical risk of recurrence. At a median follow-up of 8 years, the addition of OFS to tamoxifen in patients exposed to chemotherapy in the SOFT was associated with a 5.3% absolute benefit in disease-free survival (DFS; HR 0.76, 95% CI 0.60 to 0.97) and a 4.3% absolute benefit in overall survival (OS; HR 0.59, 95% CI 0.42 to 0.84).[8] The benefit of adding OFS was even greater in patients younger than 35 years of age at the time of diagnosis.[12] Importantly, when discussing with patients the combination of tamoxifen plus OFS, women should be made aware of the worse endocrine symptoms and sexual functioning (ie, hot flushes, loss of sexual interest, vaginal dryness and sleep disturbance) experienced with this combination particularly during the first 2 years of therapy and in those with no prior exposure to chemotherapy.[13]

While the role of OFS in premenopausal patients with higher clinical risk of recurrence (ie, those who are normally candidates also to (neo)adjuvant chemotherapy) is now well established and recommended by all major guidelines,[9–11] the best partner (tamoxifen or an AI) to be combined with OFS remains highly debated. In fact, the combination of an AI plus OFS is now considered another available treatment option for these patients.[9–11] However, the two large studies that investigated this strategy (the Austrian Breast and Colorectal Cancer Study Group 12 (ABCSG-12) trial[14] and the joint analysis of the SOFT and Tamoxifen and Exemestane Trial (TEXT)[15 16]) showed conflicting results.

In the ABCSG-12 trial, 1803 premenopausal patients at low clinical risk of recurrence (only 5% received neoadjuvant chemotherapy and none received adjuvant cytotoxic therapy) were randomised to receive OFS with goserelin plus tamoxifen or the AI anastrozole with or without zoledronic acid for 3 years.[14] With a median follow-up of approximately 8 years, no difference was observed in DFS between the two arms (HR 1.13, 95% CI 0.88 to 1.45), but OS was significantly worse in patients who received anastrozole (HR 1.63, 95% CI 1.05 to 2.52).[14] Importantly, it should be noted that differently from the SOFT and TEXT, the ABCSG-12 study included only a patients' population at low risk of relapse, administering a non-standard 3-year duration of endocrine therapy and adjuvant bisphosphonates in half of the included patients.

In the joint analysis of the SOFT and TEXT, 4690 patients were randomised to receive OFS plus tamoxifen or the AI exemestane for 5 years.[15 16] Among these patients, 57% received chemotherapy before randomisation due to higher clinical risk of recurrence (importantly, in the TEXT, OFS with triptorelin was started concomitantly with chemotherapy). Updated results at a median follow-up of 9 years showed that, in the overall study population, OFS plus exemestane significantly improved DFS (4.0% absolute benefit; HR 0.77, 95% CI 0.67 to 0.90) but no difference in OS was observed (HR 0.98, 95% CI 0.79 to 1.22). The benefit was larger in patients who received chemotherapy before adjuvant endocrine therapy.[16] To help physicians in individualising endocrine therapy decision-making, a sophisticated analysis using the non-parametric sliding-window subpopulation treatment effect pattern plot (STEPP) methodology was conducted within the SOFT and TEXT.[17] The authors examined the absolute treatment effect across a continuous composite measure of recurrence risk for each patient determined on the basis of their clinical pathological characteristics (ie, age, nodal status, tumour size, grade, oestrogen and progesterone receptors and Ki67 expression levels). This analysis showed that the greater benefit of combining OFS plus AI was observed in women with high risk of recurrence who received chemotherapy and in those who did not undergo chemotherapy but had higher-risk characteristics. The benefit of OFS plus AI over OFS plus tamoxifen was moderate in patients who received chemotherapy but had an intermediate risk of recurrence.[17]

In the treatment decision-making for the choice between OFS plus tamoxifen or an AI, it is crucial to discuss with all premenopausal patients not only the expected benefit based on the individual risk of recurrence but also the different toxicity profile of these two options, the important issue of compliance and adherence to treatment as well as the timing of administering pharmacological OFS.

The patient-reported outcomes of the SOFT and TEXT showed small and similar changes in the global quality of life indicators between the combination of OFS with tamoxifen or exemestane.[18] However, these two treatment options showed a different toxicity profile: over the 5 years of treatment, hot flushes and sweats were common with the use of tamoxifen while bone or joint pain, vaginal dryness, greater loss of sexual interest and difficulties of becoming aroused with exemestane.[18] Therefore, the different toxicity profile should be clearly discussed individually with all patients before making a final decision considering the major role that these side effects can have on their daily life.

Moreover, it should be highlighted that young patients with breast cancer have poor compliance to endocrine therapy[19]; fertility concerns are among the key factors for both non-initiation and early discontinuation of such treatment.[20 21] In the SOFT and TEXT, up to 20% of the patients stopped all protocol-assigned therapy earlier than 5 years; the rate of non-adherence to endocrine therapy was even higher for women diagnosed under the age of 35 years with 23% and 25% who interrupted triptorelin and oral endocrine therapy at 4 years, respectively.[12] On this regard, it is important to highlight that, for administering AI in premenopausal patients, a complete OFS is required while this is not the case for tamoxifen. This is an issue of crucial importance when pharmacological OFS is used. As shown in the SOFT-EST substudy, the combination of triptorelin and exemestane led to a more profound OFS than triptorelin plus tamoxifen.[22] However, up to 20% of the patients undergoing triptorelin plus exemestane had incomplete OFS during treatment; this risk seems to be higher for patients not previously exposed to chemotherapy[22] and in those with higher body mass index.[22 23] Hence, although routine monitoring of estradiol levels in patients undergoing pharmacological OFS is not recommended, when an AI is its partner of choice, physicians should be aware about the possible occurrence of physiological changes suggestive for ovarian function recovery (eg, menstrual resumption and/or cyclical fluctuations in climacteric symptoms).[9] In these cases, the AI should be changed to tamoxifen in addition to OFS. For the same reason, when compliance with monthly injection cannot be guaranteed, the combination of OFS and an AI should not be considered the best treatment approach.

Finally, regarding the timing of administering pharmacological OFS in patients who are candidates to chemotherapy, it may be considered to start its use during

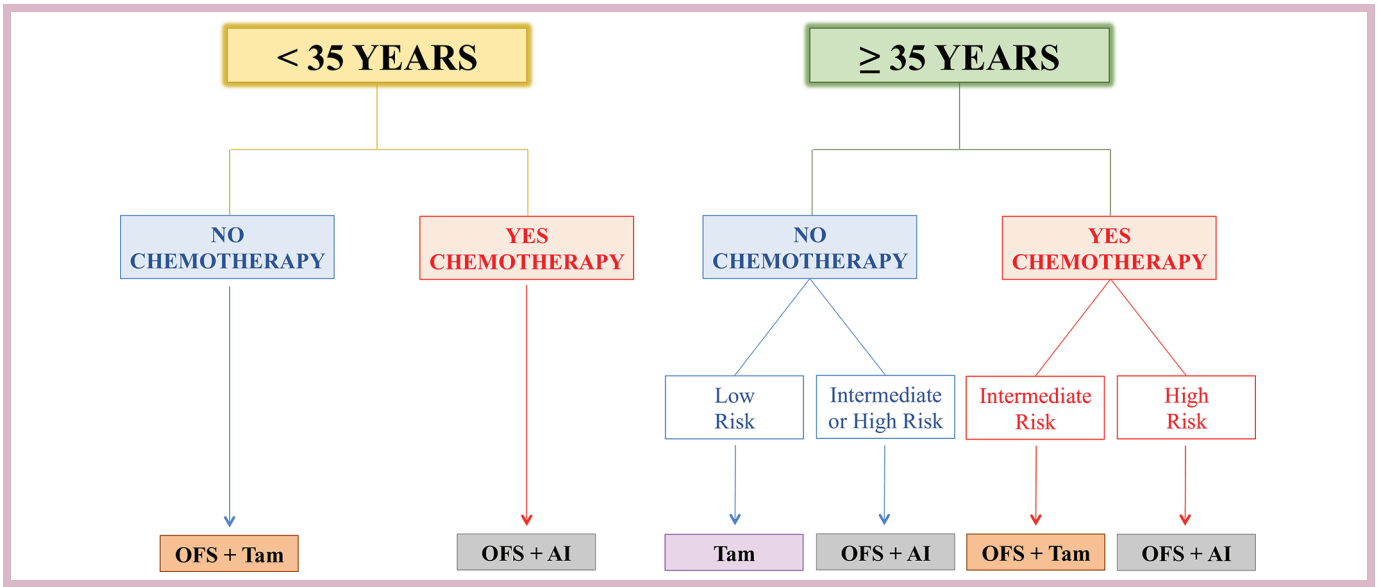

Figure 1 Algorithm for the adjuvant endocrine therapy in premenopausal patients with breast cancer. AI, aromatase inhibitor; OFS, ovarian function suppression; Tam, tamoxifen.

cytotoxic therapy instead of waiting for the end of treatment. In fact, concurrent administration of OFS and chemotherapy was shown to be safe[24 25] and has the potential to reduce the risk of treatment-induced premature ovarian insufficiency and infertility,[26–28] an issue of great importance for many young patients with breast cancer.

In conclusion, it has become rather complex to decide the best adjuvant endocrine therapy option for a given patient and even more the choice between tamoxifen or an AI when OFS is recommended (figure 1). Importantly, during treatment decision-making, patients should be adequately and extensively informed about the pros and contras of the different options; moreover, they should be closely monitored and engaged during the oncological follow-up to increase their treatment compliance and thus improving their long-term outcomes. Final results of the ongoing phase III HOrmonal adjuvant treatment BOne Effects study (ClinicalTrials.gov Identifier: NCT00412022) are awaited to give further insights on what's the best choice between tamoxifen and an AI as adjuvant endocrine therapy in premenopausal patients with breast cancer who are candidates to receive OFS.

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