The difficult decision-making process for using or not using adjuvant chemotherapy in premenopausal endocrine-responsive breast cancer patients

Available adjuvant treatments for premenopausal endocrine-responsive breast cancer patients include chemotherapy, tamoxifen and luteinizing hormone-releasing hormone (LH-RH) agonists.

In women younger than 50 years and estrogen receptor-positive (ER+) tumors, adjuvant polychemotherapy is associated with an annual reduction in mortality of 31% [standard error (SE) = 0.10]. In this subgroup of patients, tamoxifen is also very effective with an annual reduction in mortality ranging from 39% (SE = 0.12) in women younger than 40 years to 24% in women aged 40–49 years [1]. A recent meta-analysis showed that LH-RH agonists did not significantly reduce death after recurrence neither when used as the only systemic treatment [17.8% relative reduction, 95% confidence interval (CI) −52.8 to 42.9; \( P = 0.49 \)] nor when added to tamoxifen [15.9%; 95% CI −40.7 to 19.4; \( P = 0.33 \)] or to chemotherapy [12.9%; 95% CI −26.5 to 3.2; \( P = 0.11 \)] [2]. Trends observed in this meta-analysis are consistent with data from the USA Intergroup 0101 trial showing a benefit with the addition of LH-RH agonist after chemotherapy only in women younger than 40 years, supporting the hypothesis that ovarian suppression may be of benefit in younger women not achieving this with chemotherapy [3].

A controversial issue is whether both endocrine and chemotherapy treatments are necessary or whether endocrine therapy alone may be enough in premenopausal women with endocrine-responsive cancers. In women younger than 50 years with ER+ tumors, the addition of combination chemotherapy to tamoxifen achieved a highly significant death rate ratio of 0.65 (SE = 0.10) compared with tamoxifen alone [1]. Since these data can be considered as strong evidence for using both chemotherapy and endocrine therapy in premenopausal endocrine-responsive breast cancer patients, it may be surprising that the question about to give or not to give chemotherapy still arises. The main limits of the meta-analysis results are the difficulty to generalize them for all patients: the ‘average’ results could not properly fit all patients. In order to maximize the benefit and minimize toxic effects of adjuvant treatments, oncologists attempt to ‘individualize’ treatment taking into account both patient and tumor characteristics. The best way for treatment ‘individualization’ should be based on good, reliable predictors of benefit (or resistance) for any drug, allowing the oncologist to give the right drug to the right patient. Unfortunately, such predictors are not yet completely available in breast cancer. Even for endocrine therapy, only the total absence of ER and progesterone (PgR) are informative, ruling out benefit from endocrine therapy. However, the presence of even strong expression of ER and/or PgR is associated with no more than 60% probability of objective response or clinical benefit [4, 5]. The numbers are very similar for HER2 expression/amplification and response to trastuzumab [6]. For the prediction of the benefit of chemotherapy, the picture is even more complicated with no validated tools to select patients most likely to respond to the commonly used chemotherapeutic drugs. The lack of predictors of chemotherapy sensitivity could lead some oncologists to inappropriately use the presence or absence of hormone receptors in the decision making for adjuvant chemotherapy, disregarding the biological mean of hormone receptors, i.e. that they are the target of endocrine therapy and not the target of chemotherapy. Although women with estrogen receptor-negative (ER−) breast cancer benefit more from chemotherapy, as compared with women with ER+ disease [7], this latter group of patients do benefit from chemotherapy, especially if they are younger than 50 years [1]. The ER+ breast cancer population is very heterogeneous [8], and the benefit of adjuvant endocrine therapy is greater when the expression of ER is strong as compared with low expression [9, 10]. As a consequence, it could be hypothesized that in highly endocrine responsive breast cancer, endocrine therapy alone may be sufficient thus avoiding adjuvant chemotherapy also in premenopausal women [11]. Recent data, however, indicate that the benefit of modern adjuvant chemotherapy regimens, such as those including docetaxel, in patients with high expression of ER (>80%) is similar to that obtained in patients with ER− tumors. The hazard ratio for death in patients treated with docetaxel-containing chemotherapy, as compared with those not receiving docetaxel, was 0.57 (95% CI 0.37 to 0.88) in patients with ER >80% and 0.58 (95% CI 0.41 to 0.80) in patients with ER− tumors [12].

The data reported above indicate that the presence of hormone receptors, even if highly expressed, is not a reliable predictor of chemotherapy resistance and should not be a reason to rule out a potential benefit of chemotherapy when added to endocrine therapy.

The uncertainty about the tumor and patients’ characteristics to be considered in making the decision about the use of adjuvant chemotherapy may lead to adopt very different strategy in the same patient among different oncologists.

The paper of Regan et al. [13] in this issue of *Annals of Oncology* describes patient- and tumor-related factors used in
the decision-making process of whether or not to give chemotherapy in premenopausal endocrine-responsive patients who entered the phase III Tamoxifen and Exemestane Trial (TEXT). TEXT investigates the role of aromatase inhibitors compared with tamoxifen in premenopausal endocrine-responsive early breast cancer patients receiving ovarian function suppression. The decision of whether or not to use chemotherapy was determined not by the trial but by the center for each individual patient, thus providing the opportunity to investigate what factors are used in the decision-making process of whether or not to give chemotherapy in addition to combined endocrine therapy. The uncertainty still present in such a decision-making process emerges from the study results which showed that geography is one of the major determinants of chemotherapy use. The proportion of patients receiving chemotherapy varied widely according to region, ranging from 64% to 100% of those with node-positive (N+) disease and from 18% to 83% of those with node-negative (N−) disease. In particular, in North American centers where the substitution of ovarian ablation for chemotherapy is not routinely recommended to premenopausal patients [14], 52% of N− patients received chemotherapy as compared with 31% of patients from European centers of the Breast International Group. As expected, in the study of Regan et al. [13], other determinants of chemotherapy use were lymph node status (88% of N+ treated versus 46% of N−), patient age, tumor size and grade. It was only partly surprising that other biological factors such as degree of receptor positivity and HER2 status were not determinants of chemotherapy use. These results indicate that clinicians are well aware that some factors such as nodal status, patients age, tumor size and grade are strongly validated as prognostic factors while other factors such as degree of receptor positivity and HER2 status are poorly useful in predicting chemotherapy benefit, being not the target of chemotherapy but the target of endocrine therapy and trastuzumab, respectively.

The paper of Regan et al. [13] indicates that in the absence of strong predictors of chemotherapy sensitivity, the risk of relapse is considered by many clinicians as the primary determinant for using chemotherapy. In order to optimize the decision-making process for using or not using chemotherapy, our goal is to develop predictors of benefit (or resistance) for all drugs used, thus avoiding the use of poorly reliable surrogates. Although this is more complicated than we were hoping for, recent results with the use of gene expression tests are very encouraging. The 21-gene recurrence score seems able to predict benefit of both combination chemotherapy with cyclophosphamide, methotrexate and fluorouracil [15] and combination chemotherapy with cyclophosphamide, doxorubicin and fluorouracil [16] in N− and N+ endocrine-responsive early breast cancer patients receiving tamoxifen. The introduction of gene expression tests is expected to be very useful to help clinicians in choosing whether or not to add chemotherapy to endocrine therapy and in identifying which type of drugs is more likely to be active in each patient [17]. In the future, these tools will avoid that the same patient may receive very different treatment strategies depending on the center where she is referred to.

Waiting for the wide diffusion of such new tools, clinicians should continue to consider risk factors as the primary determinants for using chemotherapy in endocrine-responsive premenopausal breast cancer patients and should not forget that hormone receptors, being the targets of endocrine therapy, are not reliable predictors of chemotherapy resistance.

The days of ‘one size fits all’ therapy for patients with breast cancer are coming to an end, but the new era of ‘the right size for each patient’ is still a work in progress.

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references
