Editorial

Adjuvant Systemic Treatment Strategy for Early Breast Cancer

Franco Lumachi

Breast cancer (BC) is a common malignancy among women, with approximately 1,670,000 new BC cases each year worldwide [1]. In the USA, the incidence of BC has remained flat, with an annual decline in BC death rates of -1.9% [2]. In the European Union, the estimated death rates per 100,000 people for the years 2009 and 2015 were 15.8% and 14.2%, respectively [3]. According to the National Cancer Institute (NCI), BC that has not spread beyond the breast or the axillary lymph nodes can be defined as "early" BC [4].

Different genotypic and phenotypic features characterize BC, and gene expression patterns of cancer tissue derived from cDNA microarrays distinguish different subclasses of invasive breast carcinomas [5]. With the aim of individualizing the optimal adjuvant treatment of patients, either final surgical resection tissue or preoperative core biopsy specimen examination is required. The main data available, in addition to that obtained by routine hematoxylin-eosin stain histology, are the molecular properties of cancer cells, including the expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2), and the proliferation marker Ki67. ER, PR, and HER2 expression are evaluable by either immunohistochemical (IHC) analysis or gene amplification on fluorescence in situ hybridization (FISH) analysis, while the Ki67 rate is obtained by IHC, using the monoclonal antibody MIB-1 [6]. According to the European Society for Medical Oncology (ESMO) guidelines, the combination of these biomarkers differentiates the five main intrinsic subtypes of BC, such as luminal A, luminal B HER2-negative and HER2-positive, HER2 overexpression, and basal-like [7].

Considering the cytokeratin 5/6 (CK5/6) and the epidermal growth factor receptor (EGFR) protein expression in addition to ER and HER2 expression, another BC stratification was proposed, based on the following four subtypes: (i) luminal (ER+/HER2-), (ii) HER2 enriched (any ER expression/HER2 overexpression), (iii) basal-like (ER-/HER2-/EGFR+ and/or CK5/6+), and (iv) unclassified (ER-/HER2-/EGFR-/CK5/6-) subtype [8]. Tight junctions play a key role in the maintenance of ion flux through the cellular sheets, contributing to tissue homeostasis, and the junction proteins claudins are down-regulated by many cancer cells [9]. Based on further genome-expression studies, additional BC subtypes named claudin-low and normal-like have been identified [8-10]. There is an 80% overlap between basal-like and triple-negative BC (TNBC), which also includes particular histological subtypes of cancer, as a discordance of the molecular profile of TNBC of approximately 20% across studies has been reported [7, 8].

The College of American Pathologists and American Society of Clinical Oncology (ASCO) guidelines recommend considering the expression of ER and PR as positive when at least 1% of nuclei stain positive by IHC [12]. HER2 positivity depends on the test used. IHC results are positive (in ≥10% of cancer cells) or negative based on the quantity of HER2 protein in the cancer cells, while the FISH test reveals the HER2 gene amplification status as present *versus* absent [13]. Standardized techniques, such as automated digital image analysis (DIA) or computerized point-grid-sampling interactive morphometry (CIM) systems should be used to quantify the percentage of Ki67-positive nuclei, and it has been suggested that the optimal prognostic threshold between a low- and high-Ki67 rate ranges from 6.5% (DIA) to 9.5% (CIM) [14]. However, BCs also exhibit different biological behavior due to differences in gene expression, because the complexity of the carcinogenic process requires an integration between intrinsic molecular subtypes and morphological taxonomy, including histologic typing and grading system [15]. Thus, the concept of "intrinsic subtype" should be better clarified [15].

Adjuvant treatment of early BC requires both traditional and novel pharmacologic tools, especially in patients with TNBC who do not respond to endocrine therapy (ET). Selective estrogen receptor modulators (SERMs) block the effects of estrogens on ERs and also act as estrogen agonists in other tissues, such as bone and endometrium [16]. The main SERMs are tamoxifen, toremifene and raloxifene; the latter has been approved by the US FDA for the treatment of osteoporosis and bone mass loss [17, 18]. Aromatase inhibitors (AIs) selectively interfere with estrogens production because they antagonize the enzyme aromatase, which catalyzes the last step of hormonal synthesis (Fig. **1**).

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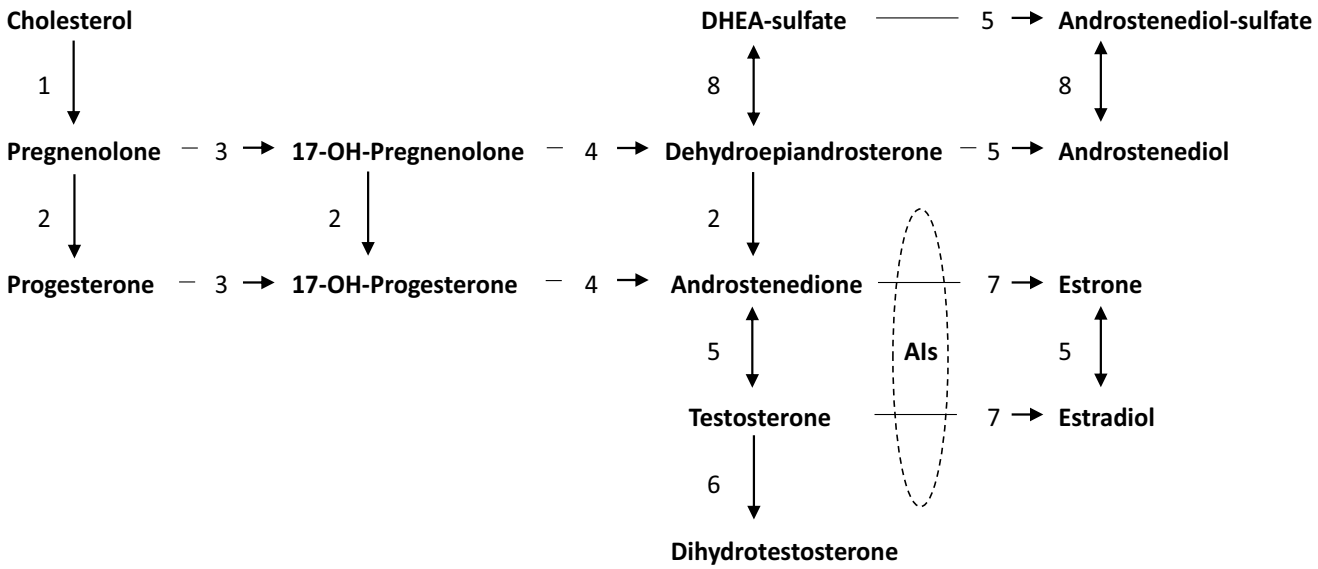

Fig. (1). Pathway of estrogens biosynthesis and enzymes catalyzing each step. 1=Cholesterol desmolase; 2=3β-Hydroxisteroid dehydrogenase; 3=17α-Hydroxylase; 4=17, 20-Lyase; 5=17β-Hydroxysteroid dehydrogenase; 6=5α-reductase; 7=Aromatase; 8=sulfatase; DHEA=dehydroepiandrosterone; AIs=aromatase inhibitors.

In premenopausal patients with luminal-type BC, tamoxifen alone or in combination with a gonadotropin-releasing hormone (GnRH) agonist is still the drug of choice. However, according to the SOFT (Suppression of Ovarian Function Trial) study, the use of a GnRH agonist in addition to tamoxifen does not provide any significant benefit [19].

Postmenopausal women can be treated with either tamoxifen or other SERMs initially (usually for 5 years before being optionally switched to AIs); they can alternatively be treated with AIs alone upfront [20, 21]. Recent studies have confirmed that upfront tamoxifen is less effective than upfront AIs, while the strategy of switching tamoxifen to AIs is less costly [22]. Patients with luminal type HER2-negative and node-negative early BC should take tamoxifen for 10 years, while those who are node-positive should be treated with tamoxifen for 5 years and then switched to letrozole for another 5 years [23].

Other drugs are available as adjuvant therapy in early BC. Bisphosphonates are drugs typically used to prevent and treat postmenopausal bone loss consequences (*e.g.,* osteopenia, osteoporosis, and pathologic fractures) and hypercalcemia [24-26]. Adding the bisphosphonate zoledronic acid to adjuvant ET may improve both disease-free survival (DFS) and overall survival (OS) of patients with BC [27, 28].

When chemotherapy is required, usually in node-positive women, no difference in OS was observed among the AC-P (doxorubicin, cyclophosphamide followed by paclitaxel), FEC-D (5-fluorouracil, epirubicin, cyclophosphamide followed by docetaxel) and dose-dense (dd) AC-P regimens, but docetaxel-related toxicity should be considered [29]. Adding gemcitabine to ddAC, did not significantly alter outcomes compared with the TAC (docetaxel, doxorubicin, cyclophosphamide) regimen [30]. In addition, the level of p53 expression should be considered a useful marker for predicting response to chemotherapy [31, 32]. In older patients (>65 years), standard CMF (cyclophosphamide, methotrexate, 5-fluorouracil) therapy exhibited similar efficacy and was better tolerated compared with docetaxel monotherapy [33].

Triple-negative BC is a heterogeneous group of aggressive breast carcinomas that are unresponsive to ET, and require individualized chemotherapeutic regimens [34]. In patients with node-positive early TNBC, TAC and CAF (cyclophosphamide, doxorubicin, 5-fluorouracil) were superior to AC-T (doxorubicin, cyclophosphamide followed by docetaxel), and the combination of carboplatin *plus* eribulin was also safe and efficacious [35, 36]. In patients with node-negative early TNBC, CMF is typically useful in reducing locoregional recurrence [37]. The TFAC (5-fluorouracil, doxorubicin, cyclophosphamide followed by paclitaxel) regimen significantly improved DFS compared with FAC (5-fluorouracil, doxorubicin, cyclophosphamide), and the long-term (10-year) OS was similar [38, 39]. In TNBC, the potential therapeutic targets are also MET (a receptor tyrosine kinase), EGFR (epidermal growth factor receptor), and SphK1 (sphingosine kinase-1) [40-42]. Further studies could eventually demonstrate the potential usefulness of such new therapies in early BC in the adjuvant setting.

Keywords: Early breast cancer, estrogen receptor, HER2, Ki67, triple-negative, adjuvant therapy, endocrine therapy, GnRH agonists, SERM, tamoxifen, aromatase inhibitors, chemotherapy, targeted therapy.

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