Adjuvant Systemic Therapies by Subtypes: Guidelines

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42.1 Introduction

The adjuvant treatment of breast cancer involves a multidisciplinary approach including surgery followed by medical treatments and radiotherapy as clinically indicated. Adjuvant systemic treatment aims to reduce the risk of breast cancer relapse, in terms of locoregional and distant events, and to prolong survival. Adjuvant treatment options for primary breast cancer include chemotherapy, endocrine therapy, biological therapy, or combination of these. Decision on adjuvant systemic therapy should be balanced on the risk of relapse, patients' comorbidities and preferences, and the potential absolute treatment benefit. It should be tailored according to tumor burden and biological behavior of cancer.

Invasive breast cancer has been historically classified according to histopathological parameters such as histomorphologic features, tumor size, nodal involvement, and presence of metastases. Recently, it has been more evident that breast cancer heterogeneity reflects a high complexity of molecular composition with different subtypes varying in their characteristics and natural history.

Perou et al. described different gene expression patterns of breast cancer. Through an extensive genomic analysis of breast cancers, authors identified four molecular subtypes (luminal A, luminal B, HER2 enriched, and basal-like) with different prognoses [1, 2].

In order to better define treatment decision, breast cancer subtypes can be defined by the use of multiparameter molecular tests such as MammaPrint (Agendia BV, Amsterdam, Netherlands), Oncotype DX (Genomic Health Inc., USA), PAM50 risk of recurrence (ROR) score (Prosigna Breast Cancer Prognostic Gene Signature Assay; NanoString Technologies, Seattle, WA), EndoPredict (EP) assay, and Breast Cancer Index [3–7]. Although in selected areas of the world multigene assays are readily available, due to their costs, their use is not possible in many countries. Surrogate pathological classification of subtypes has been studied by immunohistochemical (IHC) determination of estrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor (HER2) status, and proliferative index (Ki-67 index). Even if similar to the intrinsic subtypes, the pathological classification is not entirely the same. About 72% of triple-negative tumors are basal-like, 9% HER2 enriched, 6% luminal B, and 5% luminal A [8].

The future of breast cancer treatment is based on developing regimens that provide the greatest clinical benefit with lower side effects. Molecular diagnostic tests can provide prognostic information about cancer in its early stages. International guidelines recognize the assay's ability to predict a patient's risk of recurrence or benefit from chemotherapy. The assays are all considered usefully prognostic for years 1–5. PAM50 ROR® score is considered to be clearly prognostic beyond 5 years, whereas only Oncotype DX showed its value in predicting the usefulness of chemotherapy [9, 10, 11, 12].

According to the widely used immunohistochemistry classification of subtypes, adjuvant treatment guidelines will be examined for hormone receptor-positive HER2-negative disease that include two distinct prognostic groups, "luminal A-like" and "luminal B-like," based on Ki-67 expression level or on the expression of PgR; the "HER2-positive" group (which expresses HER2 by IHC or amplification detected by fluoresce in situ hybridization [FISH]) and the "triple-negative" group (which is negative for ER, PgR, and HER2).

42.2 Luminal-Like A and Luminal-Like B HER2-Negative Subtypes

The luminal-like subtypes are characterized by tumors that are clinically described as ER positive and a relatively high expression of many genes expressed by breast luminal cells.

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The Cancer Genome Atlas Research Network described ER-positive (luminal) breast cancers as the most heterogeneous in terms of gene expression, mutations, and copy number changes. The heterogeneity is not only for the luminal genes expression. In fact, luminal subtypes were further distinguished into at least two subgroups on the basis of their "proliferation cluster": luminal A and luminal B tumors. The proliferation cluster is a group of genes whose levels of expression correlate with cellular proliferation rates. The TP53 pathway is differently activated in this subtype, with a low TP53 mutation frequency in luminal A (12%) and a higher frequency in luminal B (29%). Other differences between luminal A and B included the hyper-activation of some transcriptional activity as c-MYC in luminal B breast cancer. This cluster also included the genes encoding the widely used immunohistochemical markers of cell proliferation as Ki-67 index [13].

The luminal A subtype of breast cancer has the best prognosis among all subtypes [2]. European guidelines define the clinicopathological surrogate of luminal A-like subtypes as those tumors with high estrogen receptor expression; low proliferation index; high progesterone receptor expression (with a suggested cutoff value of 20%); negative HER2 and a low tumor burden, meaning a lower or absent nodal involvement (N 0–3); and smaller T size (T1 or T2) [9, 12].

All luminal cancers should be treated with endocrine therapy (ET). ET is indicated in all patients with detectable ER expression (defined as ≥1% of invasive cancer cells) independently of the use of chemotherapy and/or targeted therapy. Hormonal therapies include selective estrogen receptor modulators (SERMs), such as tamoxifen, and aromatase inhibitors. The choice of agent is primarily determined by the patient's menopausal status (see Chap. 4). Other factors include side effect profiles.

It is among those luminal breast cancer patients that clinicians express highest uncertainty about optimal treatment and chemotherapy indications, as clinicians seek to avoid overtreatment and undertreatment. Results from two randomized trials of adjuvant chemoendocrine therapy for node-negative breast cancer patients showed no benefit of chemotherapy in the subgroup with high ER receptor, negative HER2, and low proliferation [14].

Moreover, the first retrospective studies with generation multigene signatures, as Oncotype DX, also showed that among patients with ER-positive breast cancer, there is no benefit of chemotherapy treatment for the low proliferative tumors. The 21-gene recurrence score (RS) assay (Oncotype DX; Genomic Health Inc., Redwood City, CA) quantifies risk of distant recurrence in patients with node-negative, estrogen receptor (ER)-positive breast cancers and has been validated retrospectively in two independent datasets. In the NSABP-B20 trial, patients with ER-positive, node-negative breast cancer were randomized to receive tamoxifen or tamoxifen plus a first-generation chemotherapy regimen (cyclophosphamide, methotrexate, and 5-fluorouracil). Chemotherapy showed a clinical benefit only in patients with high recurrence score (RS > 31) [15].

Albain et al. investigated whether the RS was prognostic in patients enrolled into the phase III SWOG-8814 trial, in which postmenopausal women with node-positive, ER-positive breast cancers were randomized to receive tamoxifen alone or tamoxifen plus a second-generation chemotherapy regimen (cyclophosphamide, adriamycin, and fluorouracil [CAF]). The study showed no benefit of CAF in patients with a low RS (score < 18; log-rank $p = 0.97$; HR 1.02, 0.54–1.93), while an improvement in DFS was seen for those with a high RS (log-rank $p = 0.033$), after adjustment for number of positive nodes [16]. This trial demonstrated that patients with high RS will benefit from chemotherapy, whereas those with low RS did not, irrespective of nodal burden.

Pending results from ongoing trials, the TAILORx trial (Trial Assigning IndividuaLized Options for Treatment) and the MINDACT trial (Microarray In Node-negative and 1–3 positive lymph node Disease may Avoid ChemoTherapy), no prospective data are available about the use of biological subtypes as eligibility criteria to adjuvant study treatment.

Recently partial results from TAILORx trial have been published with an analysis of the women in the lowest-risk group [17]. The findings showed that for the cohort of patients who had a recurrence score of 0–10 and were assigned to receive endocrine therapy alone without chemotherapy, at 5 years, in this patient population, the rate of distant relapse-free survival was 99.3%, of invasive disease-free survival was 93.8%, and of overall survival was 98.0%. These results provide prospective evidence that the gene expression test can identify women with a low risk of recurrence who can be spared chemotherapy.

On the other hand, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis from analysis of 123 randomized trials showed that taxane-plus-anthracycline-based regimens improve substantially the long-term, relapse-free, and overall survival independently by age, nodal status, tumor diameter, differentiation, and subgroup [18].

According to the available evidence, the National Comprehensive Cancer Network (NCCN) guidelines indicate to add chemotherapy to endocrine therapy for ER-positive HER2-negative node-positive disease (one or more ipsilateral lymph nodes) and for node-negative disease both for intermediate and higher recurrence score risk subgroups of patient tested by Oncotype DX test [11]. The 2015 St. Gallen Consensus report and European Society for Medical Oncology (ESMO) guidelines recommend to consider chemotherapy other than endocrine therapy not only in patients with multiparameter molecular marker at

"unfavorable prognosis" if available but also looking at clinicopathological surrogate classification for luminal-like A disease if four or more nodes are involved or if there are characteristics of luminal-like B disease, such as lower ER/PgR with clearly high Ki-67, more extensive nodal involvement, histological grade 3, extensive lymphovascular invasion, and larger T size (T3) [9, 12].

42.3 Luminal B-Like HER2-Positive Subtypes and HER2-Enriched Subtypes

The human epidermal growth factor receptor 2 (*HER2*) gene (also referred to as *ERBB2*) is amplified and/or overexpressed in approximately 15–20% of primary breast cancers.

Gene expression studies revealed that HER2-positive subtypes were characterized by an expression of several genes in HER2 amplicon and a significant frequency of TP53 mutation (71% of cases). More extensive studies with 50-gene test "PAM50" [7, 19] depicted HER2-enriched subtype as clinically HER2 positive, with high proliferation index, low expression of luminal genes, and lack of expression of basal cluster. The surrogate immunohistochemical markers to distinguish this subtype are hormone receptor-negative (ER and PgR) and HER2-positive breast cancer.

HER2-positive breast cancer could also express hormone receptors. This histopathological subtype is similar to the genome intrinsic subtype known as luminal B HER2-positive (hormone receptor positive and HER2 positive).

Overexpression of the ERBB2 oncoprotein is a well-known poor prognostic factor, and studies on clinical outcome of different subtypes revealed also that the basal-like and the HER2-positive subgroups were those with the shortest survival and relapse-free survival [2].

Trastuzumab is a recombinant humanized monoclonal antibody. The addition of trastuzumab to conventional chemotherapy in breast cancer patients overexpressing HER2 dramatically improves disease-free and overall survival in the adjuvant setting, with a 10% absolute improvement in disease-free survival (DFS) and 9% increase in 10-year overall survival (OS) [20–22].

Adjuvant treatment guidelines are unanimous to indicate chemotherapy with anthracyclines followed by a taxane-containing regimen concurrent to trastuzumab for patients with stages 2 and 3. Some specific considerations among guidelines were developed for stage 1 disease. For pT1b (tumor diameter, 0.6–1 cm) and pT1c (tumor diameter, 1.1–2 cm) tumor, chemotherapy associated to trastuzumab is also recommended [23]. The preferred chemotherapy regimen remains anthracyclines and taxane based specially for pT1c tumors, but also regimen avoiding anthracycline (paclitaxel combined to 1 year of trastuzumab) is a considerable option for pT1b tumors, based on the excellent outcome recently showed [24]. In selected cases with stage 1 disease and a very low risk, as pT1a tumor (tumor diameter 1.1–5 mm), chemotherapy and trastuzumab can be omitted.

Luminal B HER2-positive disease, differently from HER2-enriched subtype (non-luminal), requires endocrine therapy in addition to chemotherapy plus trastuzumab. Endocrine therapy should be given sequentially to chemotherapy, concomitantly to trastuzumab, and the choice of endocrine therapy should be always suggested by patient's menopausal status. No randomized trials exist to support endocrine therapy plus trastuzumab avoiding chemotherapy in this tumor subtype.

Only in selected cases of contraindications to chemotherapy or patient refusal might the combination of targeted agents (endocrine therapy and trastuzumab) be offered [12].

Based on adjuvant trials, the administration of trastuzumab should be avoided concomitantly to anthracyclines due to its cardiotoxicity (not routinely recommended outside of clinical trials) [20–22, 25], but it may be safely used concomitantly to taxane and also during radiotherapy, when indicated. It has been in fact demonstrated that trastuzumab concomitantly to taxane regimen is more effective than sequential use [21].

Standard duration of trastuzumab is 1 year according to literature data [20–22, 26, 27, 28].

No statistically significant evidence of superiority in terms of disease-free survival was observed combining dual anti-HER2 therapy including trastuzumab and lapatinib, an oral dual inhibitor of epidermal growth factor receptor (EGFR) and HER2 tyrosine kinases [29].

42.4 Triple-Negative Subtype

Among breast cancer subtypes, gene expression array study identified the basal epithelial cells that expressed a characteristic gene cluster including keratin 5, keratin 17, integrin beta 4, and laminin. These tumors also showed a lack of ER and most of the other genes that were usually co-expressed with estrogen receptors [1].

Basal phenotype is defined as negative for hormone receptors and HER2 and positive for cytokeratin 5/6 or epidermal growth factor receptor; it represents a different clinical entity associated to highest TP53 mutations and shorter survival times with a 5-year survival rate of 79.0% (70.8–85.3) and a 73.5% disease-free survival at 5 years (65.0–80.5) [2, 30].

Randomized controlled trials and retrospective studies evaluating the correlation between chemotherapy benefit and ER status suggest that the magnitude of the benefit of chemotherapy is large in patients with ER-negative subtypes

[18, 31]. Due to the absence of known specific therapeutic target, chemotherapy is the standard indication of the international guidelines favoring anthracyclines and taxane-based regimens [9, 11, 13].

Classical cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) is reported as effective for the treatment of TNBC and may still be used in selected cases [14, 32].

Controversies exist about the use of anthracycline and taxane dose-dense schedules (with granulocyte colony-stimulating factor support) [33, 9, 11, 13] although this treatment can be regarded as a reasonable option, particularly in highly proliferative tumors.

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