REVIEW

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"Triple positive" breast cancer – a novel category?

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Abstract

Breast cancer (BC) biology is of outmost importance for its therapeutic management and for establishing patients' outcome. Breast cancer has been divided in subtypes depending on the presence of hormone receptors (HRs) for estrogen and progesterone and human epidermal growth factor receptor 2 (HER2) gene amplification. Recently, a distinct subcategory has been analyzed from the group of HER2-enriched BC with positive HR, namely HER2 positive with high levels of hormone receptor expression, suggestively named "triple positive" breast cancer. We aim to review current evidence on this subtype of BC, from the molecular mechanisms regulating its behavior to the current standard treatment outcome in order to establish whether it qualifies as a new distinct subtype of BC. Its biology is dominated by the crosstalks between HR pathway and HER2 pathway, which might be responsible for the development of rapid resistance to treatment, because of estrogen receptor up-regulation and alternate regulatory pathways activation when anti-HER2 agents are used. "Triple positive" subtype has apparently similar outcome when treated with chemotherapy alone, compared to chemotherapy and anti-HER2 agents treatment. It resembles more to luminal A breast cancer, with positive HR and HER2 negative. However, most of the clinical evidence is provided by retrospective trials with multiple potential biases. Treatment of "triple positive" subtype of BC with anti-HER2 agents and chemotherapy remain standard until stronger evidence will be available. Whether "triple positive" category should be regarded as a separate entity with distinct characteristics and management has to be demonstrated in future better designed trials.

Keywords: breast cancer, hormone receptors, triple positive, growth factor receptor, immunohistochemistry.

Background and molecular basis

Breast cancer (BC) involves multiple abnormal regulation pathways, dominated by estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) signaling pathways. Current research identified the presence of numerous crosstalks between the two capital pathways, enabling cancer cells to become resistant to chemotherapy or hormone therapy; blocking one pathway augments and up-regulates other alternate pathways [1, 2]. Encouraging results have been obtained with double blockade, consisting of anti-HER2 agents and hormonal therapy [3].

Initially, HER2-positive tumors were associated with negative hormone receptors (HRs), but thereafter it was shown that about half of the HER2-enriched BC patients had HR positive to some extent, usually expressed at low levels. BC overexpressing HER2 was found in 21% of tumors with estrogen receptor (ER)+/progesterone receptor (PR)- and in 14% of tumors with ER+/PR+ in a large trial [4].

It has been proved that HER2-enriched breast cancer patients have usually a worse prognosis and decreased survival rates compared with HER2-negative patients [5, 6]. For HER2-positive breast cancer, anti-HER2 agents are now standard therapy and are usually associated with chemotherapy to effectively control disease progression; hormonal therapy fails frequently to improve outcome in patients with positive hormone receptors (HRs+) and HER2-positive disease [7]. Functional crosstalks between endocrine and HER pathways might be involved to ease resistance to anticancer therapy. Recently, HER2-positive breast cancer tumors with HR+ were divided in subgroups and analyzed; differences in behavior and response to treatment were observed when high levels of HR were found compared to low HR expression in patients with HER2-enriched breast cancer. The concept of "triple positive" breast cancer, defined by high level expressing HR of HER2 positive breast cancer, emerged, with distinct response to conventional treatment [8]. The question raised is whether "triple positive" breast cancer is behaving rather like HR positive HER2 negative breast cancer and its treatment should be individualized accordingly.

The idea of separating a group from the breast cancer patients with HER2-enriched disease and positive hormone receptors with high levels of hormone receptors, more similar to luminal A subtype is still debated. The aim of our review is to discuss existing clinical evidence regarding particular behavior and distinct outcomes of patients with HER2-amplified breast cancer and high levels of HR, which would constitute strong arguments for a novel BC subtype.

Histopatological classifications

Expression of ER, PR and HER2 divided initially breast cancer in three subtypes: hormone receptor positive (HR+; ER and/or PR positive), HER2 positive (HER2+) and triple negative (TNBC; ER, PR and HER2 negative) subtypes, with different therapy approaches and individualized behavior. Subsequently, the molecular tumor profiling has enabled a more detailed classification, based on gene expression, each category with distinct management. There are five subtypes of breast cancer in the molecular classification, comprising of luminal A (hormone receptor positive, HER2-, lower proliferating index, 30–40% of all BC), luminal B (lower levels of positive estrogen receptor or progesterone receptor negative, sometimes with HER2+, higher proliferating index, 30–40% of all BC), HER2-enriched category (hormone receptor negative, HER2+, 15–25% of BC), basal-like subtype (usually triple negative, 10–20% of BC) and claudin-low subtype, less reproducibly defined yet (usually triple negative, 10–15% of BC) [9–13].

Immunohistochemical classification of breast cancer is important because it correlates with chemotherapy, hormone therapy and targeted agents response of BC subtypes and has prognostic significance. It has been clearly stated for example that a key role in aggressive BC subtypes (luminal B or basal-like subtypes) is played by anthracycline-based chemotherapy, followed, apparently paradoxically, more frequently by pathological complete response in neoadjuvant setting than in luminal A breast cancer cases. Worse overall outcomes for the aggressive subtypes would be due to the possibility of recurrence that is higher for aggressive BC subtypes [14]. The first two categories, luminal A and B, have predictive role on the 10-year outcome and the risk of distant recurrences after five years of hormone therapy. Independent of adjuvant treatment type, luminal B is followed by worse outcomes than luminal A.

"Triple positive" subtype was delineated from the HER2-enriched BC with high levels of ER and PR, which forms a minority of cases (most of HER2+ have low levels of HR when positive). The following figures represent a typical "triple positive" BC with highly expressing levels of all receptor types. Figure 1 presents Hematoxylin–Eosin (HE) staining of invasive ductal carcinoma of no special type (IDC–NST). Figure 2 shows immunohistochemistry with 70% positive ER, while Figure 3 represents a proportion of 50% positive PR. Figures 4 and 5 reveal HER2 status at immunohistochemistry exam and confirmation with silver *in situ* hybridization (SISH).

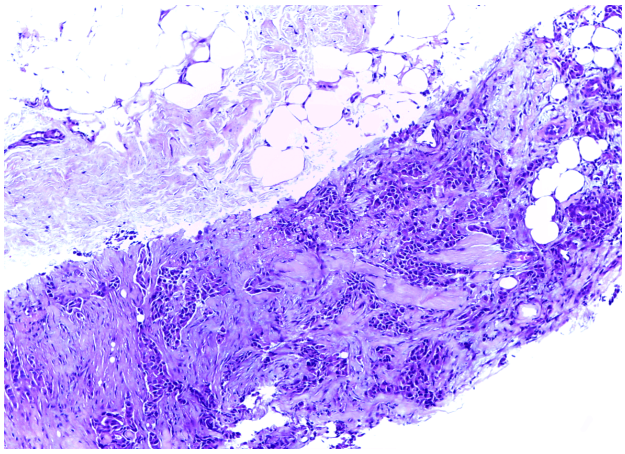

Figure 1 – ***Invasive ductal carcinoma of no special type (IDC–NST). HE staining, ×100 (OncoTeam Diagnostic® private collection, reproduced with permission).***

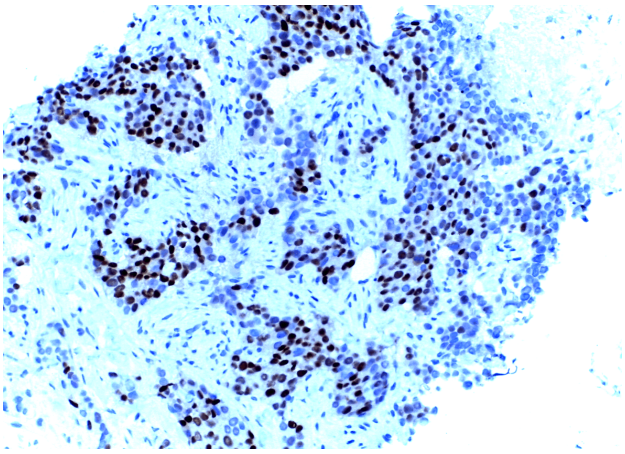

Figure 2 – ***IDC–NST: estrogen receptor (ER) positive in 70% cells. Immunohistochemistry, ×200 (OncoTeam Diagnostic® private collection, reproduced with permission).***

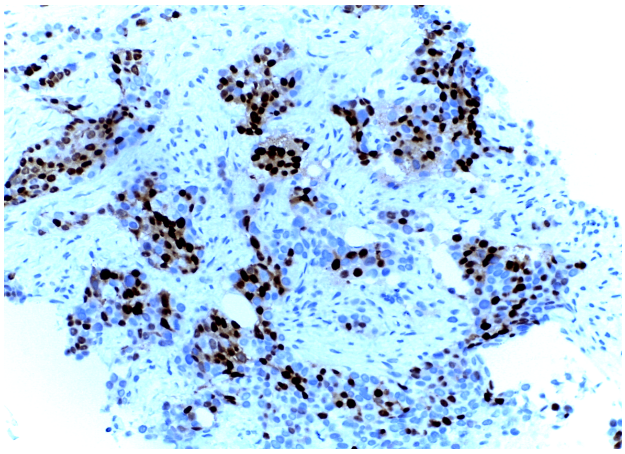

Figure 3 – ***IDC–NST: progesterone receptor (PR) positive in 50% cells. Immunohistochemistry, ×200 (OncoTeam Diagnostic® private collection, reproduced with permission).***

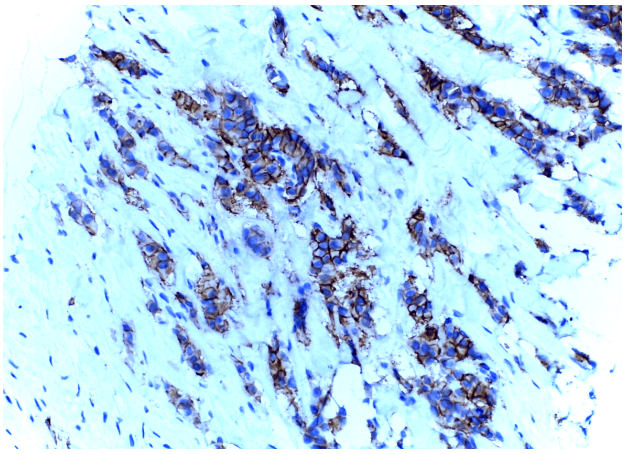

Figure 4 – ***IDC–NST: Cerb-B2 2+. Immunohistochemistry, ×200 (OncoTeam Diagnostic® private collection, reproduced with permission).***

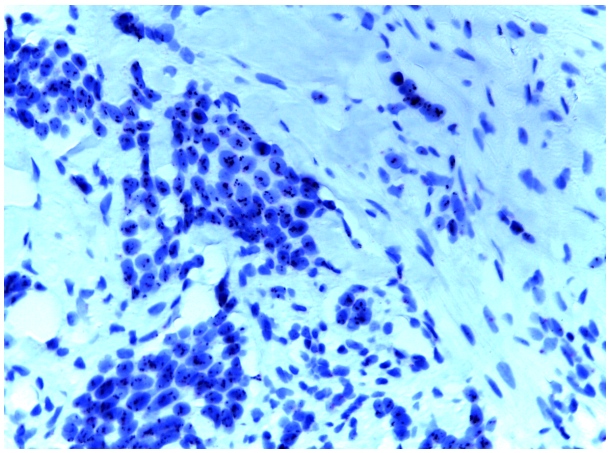

Figure 5 – ***IDC–NST: HER2 amplified. Silver in situ hybridization (SISH), ×400 (OncoTeam Diagnostic® private collection, reproduced with permission).***

Other breast cancer subtypes have been proposed as single standing categories over time, but did not make it to distinct subtypes with individual management in standard classifications. An example is apocrine carcinoma defined as a subtype of IDC with positive androgen receptors (ARs) and often negative estrogen and progesterone receptors, with aggressive behavior similar to basal-like breast cancer [15, 16]. Anti-androgen therapy was promoted to improve BC therapy in patients with BC and positive AR [17–19]. However, a meta-analysis showed better overall survival and disease-free survival in patients with positive ARs irrespective of the presence or absence of estrogen receptors [20]. In the category of triple negative breast cancer (TNBC), quadruple negative breast cancer was proposed as a distinct subtype with additional negative ARs and with similar basal-like BC behavior, while the rest of TNBC to be classified as AR+ TNBC [21, 22].

Relevant molecular interaction and clinical significance

There is plenty of clinical evidence to prove a particular behavior of "triple positive" breast cancer cells that develops more frequently resistance to administered therapy.

ER and HER2 pathways are the main mechanisms involved in pathogenesis of breast cancer growth and most targeted by the current treatments; this fact is reflected by the classifications mentioned above. Although very effective in selected group of patients, there is still a high burden of patients that develop resistance to treatment and are difficult to manage with subsequent agents. It is well known that numerous crosstalks between ER and HER pathways contribute to the development of therapy resistance in breast cancer [23]. ER-targeted inhibitory therapy is widely used with proved clinical efficacy, improved outcomes and increased cure rate, though still with frequent resistance development [24]. Resistance to tamoxifen is mediated with aid of epidermal growth factor receptors like EGFR/HER2 family, frequently overexpressed in breast cancer patients resistant to hormonal therapy and enhancing crosstalks with ER pathway [25, 26].

Consequently, numerous crosstalks between ER and HER pathways lead often to upregulation of one pathway when the other one is inhibited [1]. It was shown that endocrine treatment with aromatase inhibitors was followed by an increase in HER2 mRNA in tumors that originally were not HER2-enriched [2]. Next step was the research of combined treatments blocking both signaling pathways and results are promising. Anastrozole and anti-HER2 agent trastuzumab combined therapy was researched with good results, though still under expectances [3]; lapatinib, an anti-EGFR agent, trastuzumab and letrozole provided good results in locally advanced HER2+/ER+ breast cancer [27]. Encouraging results were obtained with anti-EGFR agent gefitinib and hormonal therapy, either tamoxifen or anastrozole [28, 29].

"Triple positive" breast cancer clinical trials

A recent multicenter large retrospective clinical trial enrolling early breast cancer patients with ER/PR and HER2-positive assessed treatment outcomes, depending on HRs expression. Adjuvant treatment outcomes of patients treated with chemotherapy alone or chemotherapy plus trastuzumab were compared. Authors evaluated specifically subpopulations with hormone receptors positive in >30% of cells and in >50% of cells. Although overall, in the whole population analyzed, trastuzumab improved relapse free survival (RFS) and breast cancer specific survival (BCSS), when selected subpopulations were analyzed, there was no improvement of adding trastuzumab to chemotherapy when considering BCSS in subpopulation with >30% HR+ and when considering RFS in subpopulation with >50% HR+ [30]. Results were in concordance with the described crosstalks between HER and ER pathways. Trastuzumab efficacy is reduced in patients with high levels of ER expression due to upregulation of ER pathways which raises questions regarding efficacy of trastuzumab in "triple positive" breast cancer. At this point, "triple positive" BC might be rather assimilated to HR+ and HER2 negative luminal classification tumors, than to HER2-enriched BC that would benefit of anti-HER2 agents. Previous RETROHER clinical trial provided similar results [31]. However, possible biases are related to retrospective design of the trial, to the sequentiality and non-concomitance of the two cohorts, with significant differences of follow-up between groups, which might be responsible of the differences in outcomes. Selection bias concerning histopathology characteristics are another weak point; cohort B had more often high HRs levels and higher stage, higher grade and higher proliferating index compared with cohort A. HRs levels were extracted from the medical documents from different centers so selection biases and inter-laboratory variability could not be avoided. Other molecular changes should have been considered as well: EGFR and phosphatase and tensin homolog (PTEN) expression, PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) mutations, lymphocyte tumor infiltration [31].

Breast cancer patients with HR and HER2-positive disease at high risk of recurrence are usually treated in adjuvant setting with trastuzumab as anti-HER2 agent and with chemotherapy and endocrine therapy. When

metastases are identified, trastuzumab is associated usually with chemotherapy; frequently, better results are obtained in ER-negative and HER2-positive patients, when compared to ER-positive patients [32]. On the other hand, patients receiving trastuzumab and an aromatase inhibitor experienced progression late, at more than two years, suggesting that blocking both pathways and their crosstalks might delay initiation of chemotherapy [3]. However, unfortunately no clinical trials are available to compare combined treatment with trastuzumab and chemotherapy *versus* trastuzumab and endocrine therapy, to assess a potential associative effect of anti-HER2 agents and hormonal therapy. Hormonal therapy combined with anti-HER agents in "triple positive" patients could be the key because of the good safety profile and apparently good efficacy. Hormone therapy alone is to be considered with caution because of the insufficiently existing data and the risks of suboptimal blockade. Endocrine therapy is tempting for patients with significant comorbidities and low volume disease or slowly progressive [33].

Assessment of this new distinct subtype of HR+ HER2+ breast cancer raises a series of problems. First of all, it is the ethical difficulty to design a prospective clinical trial to enroll patients with HER2+ HR+ breast cancer ("triple positive") with an arm that should not receive anti-HER2 agents (which are currently the standard), but only chemotherapy to verify the hypothesis of similar outcomes with patients receiving anti-HER2 agents and chemotherapy. Secondary, targeted agents have good safety profile and many biosimilar molecules are available, making them easily accessible and are standard treatment for HER2+ patients [34]; anti-HER2 agents, especially trastuzumab, have many studies behind proving their efficacy in prolonging survival in patients with HER2-enriched breast cancer, in incipient and advanced BC as well [35, 36].

Dual blockade with trastuzumab and pertuzumab has already received accelerated approval in neoadjuvant setting of HER2-enriched BC treatment, based through others mainly on two large trials showing increased pathological complete response rates by adding pertuzumab to trastuzumab – 45.8% *vs.* 29% in NeoSphere [37] and 57.3% to 66.2% with different cytostatic agents, containing the two anti-HER2 molecules in TRYPHAENA trial [38]. Additionally, new data is on the way to be published regarding increased efficacy of dual blockade of HER2 with trastuzumab and pertuzumab together with chemotherapy in adjuvant setting (APHINITY trial), which will make even more difficult to leave aside HER2 blockade in "triple positive" subset of BC patients [39].

Conclusions

Appropriate immunohistochemical subtyping of breast cancer patients is important for establishing optimal treatment regimen and subsequently better outcomes. "Triple positive" breast cancer subtype consisting of high levels of HER2, estrogen and progesterone receptors expression seems promising in better understanding and treating BC patients. Adjuvant trastuzumab might not add supplementary benefit to chemotherapy in "triple positive" BC. Additionally, these patients might rather benefit of endocrine therapy combined with anti-HER2 agents, without chemotherapy. However, there is not enough solid clinical evidence to date to change the standard management of this category. Whether "triple positive" breast cancer is indeed a distinct subtype, with individualized treatment and outcomes, will have to be established in future, by better designed clinical trials.

Conflict of interests

The authors declare that they have no conflict of interests.

Acknowledgments

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