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Invasive lobular breast cancer and its variants: How special are they for systemic therapy decisions?

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Abstract

The WHO classification of breast tumors distinguishes, besides invasive breast cancer 'of no special type' (former invasive ductal carcinoma, representing 60–70% of all breast cancers), 30 special types, of which invasive lobular carcinoma (ILC) is the most common (5–15%). We review the literature on (i) the specificity and heterogeneity of ILC biology as documented by various analytical techniques, including the results of molecular testing for risk of recurrence; (ii) the impact of lobular histology on prediction of prognosis and effect of systemic therapies in patients. Though it is generally admitted that ILC has a better prognosis than IDC, is endocrine responsive, and responds poorly to chemotherapy, currently available data do not unanimously support these assumptions. This review demonstrates some lack of specific data and a need for improving clinical research design to allow oncologists to make informed systemic therapy decisions in patients with ILC. Importantly, future studies should compare various endpoints in ILC breast cancer patients among the group of hormonosensitive breast cancer.

Keywords: Invasive breast cancer; Invasive lobular carcinoma; Pleomorphic invasive lobular carcinoma; Tubulo-lobular carcinoma; Prognosis; Predictive factor; Luminal breast cancer

1. Introduction

Breast cancer (BC) is a biologically heterogeneous disease encompassing subgroups associated with different epidemiology, natural history and response to systemic therapies [1]. Over the last decade, the BC community has shifted toward an understanding of this heterogeneity along the intrinsic subtypes generated in 2000 by unsupervised clustering of gene expression patterns generated by complementary DNA microarrays (*e.g.* luminal A and B, HER2-enriched, and basal-like) [2,3]. Current guidelines for systemic therapy decisions acknowledge four main subgroups of BC corresponding to these four main molecular classes that are determined by the presence/absence of targets for available therapeutic approaches. These targets are evaluated using morphological methods such as immunohistochemistry (IHC) for hormone receptors (HR), HER2 and Ki-67 protein expression, and *in situ* hybridization techniques (ISH) for HER2 gene amplification [3].

Histological types, based on BC morphology as observed under the optic microscope, represent a classical approach to describe BC heterogeneity. The 2012 WHO classification distinguishes, besides invasive BC 'of no special type' (former invasive ductal carcinoma (IDC), representing about 60–75% of all BC), 30 special types and subtypes, of which invasive lobular carcinoma (ILC) is the most common, representing 5–15% of all BC [1]. It has been long recognized that all BC, lobular and non-lobular, arise from the terminal duct lobular unit, thus the term lobular no longer designates its origin [4]. Most ILC express estrogen (ER) and/or progesterone (PR) receptors and thus belong to the luminal intrinsic molecular subgroup of BC [1].

The importance of individualizing this subgroup of BC lies in its incidence and its biological and clinical specificities. ILC incidence has increased over the past two decades especially in women over 50 [5,6]. This increase has been correlated to the use of hormone replacement therapies, especially regimens containing progesterone [7,8]. It is important to stress that given the high overall incidence of BC worldwide, the current incidence of this most frequent subtype of BC is comparable to the one of brain tumors or myeloma [9].

The relevance of the individualization of the lobular subtype of BC has been challenged by some authors after genetic studies demonstrated common consistent abnormalities shared by *low grade* BC (ductal as well as lobular) (1q gain, 16q loss), as opposed to *high grade* BC (p53 mutations, 17q gains) [10–12]. The arguments in favor of conserving the lobular special type include the high incidence of loss of expression of the cell-cell adhesion molecule E-cadherin, not observed in other low grade BC, and the peculiarities of clinical presentation and metastatic pattern: peritoneum and retroperitoneum, hollow viscera, internal genital organs, leptomeninges (besides common bone metastases) [1,13–18].

Heterogeneity has long been recognized among *in situ* as well as invasive lobular BC. Classic-ILC is characterized by monotonous small, round, discohesive cells growing in linear strands (so called 'indian files') and forming target figures around ducts either preserved or involved by *in situ* lobular neoplasia (Fig. 1) [1]. The cytoplasm is pale or eosinophilic and may contain a small pink vacuole. The nuclear pleomorphism (*e.g.* nuclear size, shape, hyperchromatism, nucleoli) is low to moderate (Fig. 1). Mitotic figures are sparse. Host reaction varies from none to abundant fibrosis. ILC is commonly admixed with an *in situ* component that may be of lobular (lobular *in situ* carcinoma/lobular neoplasia) but also of low grade ductal type [11]. Morphological variants differ from the classic form either by their architectural pattern of growth (solid, alveolar, and trabecular variants) or by their cytology (pleomorphic, apocrine, histiocytoid, signet ring cell variants) [19–21]. Based on pattern of growth at low