Invasive lobular breast cancer: critical issues and emerging options

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Abstract

Invasive lobular carcinoma represents a unique entity of breast cancer with peculiar pathological and clinical features, which are different to the more common invasive ductal carcinoma. Indeed, emerging evidences suggest differences in both the metastatic and recurrence pattern and, above all, in the treatment sensitivity, with particular regard to chemotherapy. Nevertheless, the treatment decision of invasive lobular carcinoma is based upon data as a subgroup of trials where the large majority of patients were affected by a different histology. In this review, an overview of the literature about invasive lobular carcinoma is provided, aiming to investigate the role of emerging predictive and prognostic factors and to analyze the new therapeutic opportunities.

KEY WORDS: lobular, breast cancer, review.

Introduction

Invasive lobular carcinoma (ILC) represents the second most common histological subtype of breast cancer after invasive ductal carcinoma (IDC), with an incidence approximately of 5-15% according to the different clinical records. This wide discrepancy might be attributable not only to variations in patients' populations, but also to the use of different diagnostic criteria (1). The data coming from the Surveillance, Epidemiology, and End Results Program (SEER) database show a different distribution of ILC according to ethnicity, with a higher incidence for Caucasian women (9.4%) and a lower for Asian-Pacific (5.3%). Besides, while the incidence of IDC not otherwise specified (NAS) stayed stable over time, the incidence of ILC is constantly increasing, particularly among post-menopausal women, probably due to the wide use of hormone replacement therapy, which, as well as for the alcohol consumption, is associated with a 2.0-3.9 fold-increased risk of malignancy (2, 3).

A peculiar clinical, radiological, pathological and biological pattern defines ILC and differentiate that from the most common IDC. The purpose of the present review is to highlight the characteristics, the prognosis and the treatment opportunities of ILC.

Methods

A computed literature search was conducted using Medline (Pubmed) website searches. Deadline for trial publication and/or presentation was May 30th, 2014. In addition to Medline search, ASCO (American Society of Clinical Oncology, http://www.asco.org), ESMO (European Society for Medical Oncology, http://www.esmo.org), SABCS (San Antonio Breast Cancer Symposium, http://www.sabcs.org) websites were browsed. Key-words used for searching were: ‘lobular, breast cancer, carcinoma’. Furthermore, lectures at major meetings (ASCO, ESMO, SABCS) having breast cancer as the topic were checked. No language restriction were applied.

Anatomo-pathological features

The classic (or pure) aspect of ILC (30-75%) is characterized by non-cohesive small and uniform cells which invade the stroma as a ‘single-file’ pattern or appear individually dispersed without any cohesion; these cells tend to grow in a circumferential manner around ducts and lobules with little host desmoplastic reaction. Diff-
ferently, ILC with ductal features is currently classified as a mixed invasive lobular and ductal carcinoma (2-5%). In absence of a diffuse nonlinear growth pattern, variants forms could be identified, including alveolar (g lobular aggregates), solid (solid sheets of uniform cells), tubule-lobular (small, uniform cells in a linear pattern with tubular glands, low grade), signet-ring cells and pleomorphic subtypes (higher cellular atypia, nuclear pleomorphism, higher mitotic frequency). Both solid and pleomorphic subtypes show more aggressive clinical behavior in contrast with tubulo-lobular carcinoma, that has an excellent prognosis (4-6).

Moreover, ILC has less vessel invasion and a lower grade at histology, in comparison with IDC. However, the Nottingham combined grading system is not currently considered appropriate by the large majority of the pathologists, because it takes into account tubules formation which does not usually occur in case of ILC (7). Given the aspects of ILC, both the cytological diagnosis by fine needle aspiration and the histological diagnosis by needle core biopsy are difficult, with a failure rate for detection ranging from 4 to 40%, depending on the different series (8). In this regard, the achievement of a correct diagnosis may be facilitated with the integration of pathological and molecular features with radiological and clinical aspects.

Clinical and radiological features

Lobular breast carcinoma is associated with older age at presentation, greater diameter and multifocal aspects. Older studies show a two-fold increase in bilaterality (9). However, recent analysis do not report any difference for ILC compared to IDC (10, 11). Lymph-node involvement is similar or lower than IDC (12). The clinically and radiological identification of ILC is challenging and difficult, given the diffuse growth pattern and the less desmoplastic reaction. In this regard, mammography may determine a high false-negative rate (13, 14), with remarkable implications for the screening. Both clinical examination and mammography could underestimate the real size of the lesions. Magnetic resonance could be helpful, in particular for the preoperative assessment of ILC (15).

Molecular features

Invasive lobular breast carcinoma tends to have a lower rate of aggressiveness features, such as aneuploidy, high S-phase fraction and expression of p53, ERBB2 and EGFR (9). Estrogen-receptors (ER) are often positive and androgen-receptors are usually identified (90%). HER2 is frequently not overexpressed. The most frequent genetic alteration of ILC is the loss of 16q, where the E-cadherin gene (CDH1) is located, due to loss of heterozygosity or methylation. E-cadherin is a glycoprotein that mediates the adhesion between the epithelial cells, which suppress the invasion and metastasis and play a key role in a series of cellular processes, including the cell development, migration, polarity and tissue integrity. The loss of E-cadherin expression characterizes 85% of lobular breast carcinoma and it is usually adopted by pathologists to confirm the diagnosis of ILC. It has also been proposed to represent an important step in lobular tumor carcinogenesis and to be the factor responsible for its distinct morphology, pattern of invasion and metastatic behavior (12, 16).

Moreover, asporine, a cartilage extracellular protein and CT1RC1 (collagen triple helix repeat containing 1) are upregulated in lobular breast cancer and may have a role in the association between E-cadherin and the diagnosis of ILC (17).

The pleomorphic variant shows the amplification of the oncogenes MYC and ERBB2, which contribute to justify the aggressive clinical behavior of such subtype.

Recurrence, metastatic pattern and prognosis

Invasive lobular breast cancer differs from IDC for the metastatic patterns as well. While IDC tends to usually spread to pleura and lung, lobular breast carcinoma is associated with a higher rate of bone, gastrointestinal, peritoneal, ovarian and skin secondary metastases (12, 18).

The evidences concerning the prognosis of ILC compared to IDC are controversial. Indeed, older studies have concluded that ILC has a better prognosis compared to IDC (19, 20). Two recent studies with a prolonged follow-up have shown that the effect of histological type varies across time, with an initial favorable impact of ILC on disease free survival (DFS) and overall survival (OS). After 6 years, the risk of relapse event increases for ILC (10). This behavior is likely to be correlated to the indolent nature of the disease and the lower use of adjuvant therapy, but seems to be independent by the hormonal receptor (HR) status (21). Moreover, a more favorable outcome is reported for classic ILC than for variants, with a worse outcome for pleomorphic ILC and a better prognosis for alveolar and tubular types (22, 23).

These evidences are not confirmed in other studies, where short and long-term outcomes appear similar, remaining better than IDC (24).

Local treatment

Mastectomy is the more frequently used surgical approach for ILC. Moreover, the rate of conversion from breast conserving surgery (BCS) to mastectomy is in-
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The larger diameter at diagnosis, the histological features of lobular carcinoma and the related difficult in the definition of clinical and radiological tumor margins may significantly contribute to increase the rate of the wider surgical excision.

Prognostic factors

Several studies have suggested a series of biomarkers as potential prognostic determinants for ILC. Cycline D1 is a protein responsible for driving G1 to S-phase transition in the cell cycle. Aberrant cycline D1 expression in the breast is consistently associated with oncogenic properties. Tobin et al. found that protein in 96% of lobular breast carcinoma, and its overexpression was associated with worst recurrence-free survival (RFS). No stromal expression was noted and its presence in non-tumor cells was rare (25). A series of potential prognostic factors for ILC is reported in Table 1. Survivin is one of the eight inhibitor of apoptosis (IAP proteins), interferes with the initiator caspase-9 and the effectors caspase-3 and caspase-9; regulates cell division and enhances angiogenesis (26). Survivin overexpression inducts an aberrant progression of the transformed cells through mitosis and is found in 86% of ILC, with a predominance of nuclear and combined nuclear and cytoplasmic immunoreactions. It appears to be an independent prognostic factor in ILC with its overexpression associated with a worse prognosis. It seems also to be correlated with HR expression. Nevertheless, conflicting data have been reported on the prognostic role of survivin in breast cancer (27).

Mutational analysis revealed a very high frequency of PIK3CA somatic mutation for ILC, with a mean mutation rate of 40% across different studies (28, 29). Other authors, who applied more stringent criteria for ILC diagnosis, including lack of E-cadherin expression, observed a lower rate of PIK3CA mutations in such subgroups. Christgen et al. suggested a role of PIK3CA mutations in ILC progression to local recurrence but not for distant metastases, according to those evidences showing an approximately two-fold increase in local recurrence with respect to the primary tumor and the absence of distant metastases. This is also independently associated with an increased risk of death (30).

The fibroblast-growth-factor receptor-1 (FGFR-1) belongs to the family of those tyrosine kinase triggering the signaling involved in the proliferation, the differentiation and the epithelial to mesenchymal transition. A subset of primary and metastatic lobular carcinoma harbors FGFR-1 gene amplification (31), which can lead to a poor prognosis in luminal-type breast cancer (32).

The prognostic role of the insulin-receptor-substrate-1 (IRS-1) and the transcription factor E2F1 is still under debate. The overexpression or downregulation of IRS-1 and insulin-growth-factor-receptor-1 (IGFR-1) are implicated in breast cancer development and progression through multiple antiapoptotic, growth promoting and prometastatic pathways. A correlation of IRS-1 and Ki67 was found, with a higher expression in ILC with a moderate and undifferentiated tumor grading (33). Mercaipide et al. demonstrated an inverse correlation between the transcription factor E2F1 and the tumor grading in ILC, without a clear relationship with prognosis.

Predictive factors

A list of potential predictive factors for ILC is reported in Table 2. Mutations in exon 9 of PIK3CA gene are more frequent in ILC and are associated with an increased resistance to paclitaxel in particular (34). FGFR1 and its ligand FGF2 are involved in the response to chemo-radiotherapy. Massabeau et al. found that among ILC with a well-differentiated and moderate tumor grading, those with a negative expression of FGFR-1 did not respond to chemo-radiotherapy. Moreover, Turner et al. showed that the amplification and overexpression of FGFR1 may determine endocrine therapy resistance (32).

Table 1 - Prognostic factors under investigation in ILC.

<table>
<thead>
<tr>
<th>Prognostic factors</th>
<th>Role</th>
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<tr>
<td>Cicline D1</td>
<td>Overexpression associated with reduced RFS</td>
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<tr>
<td>Survivin</td>
<td>Overexpression associated with worse prognosis</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>Mutation associated with local recurrence and death</td>
</tr>
<tr>
<td>FGFR-1</td>
<td>Amplification associated with poor prognosis in luminal-type breast cancer</td>
</tr>
<tr>
<td>IRS-1</td>
<td>Higher expression found in G3 tumors; correlation with Ki67</td>
</tr>
<tr>
<td>E2F-1</td>
<td>Inverse correlation with tumor grade</td>
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Table 2 - Predictive factors under investigation in ILC.

<table>
<thead>
<tr>
<th>Predictive factors</th>
<th>Role</th>
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<tbody>
<tr>
<td>Topoisomerase II-a</td>
<td>Absent amplification associated with anthracyclines therapy resistance</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>Mutation in exon 9 associated with an increased resistance to paclitaxel</td>
</tr>
<tr>
<td>FGFR-1</td>
<td>Negative expression associated with absent response to chemoradiotherapy</td>
</tr>
<tr>
<td></td>
<td>Amplification or overexpression associated with endocrine therapy resistance</td>
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</table>
Invasive lobular carcinoma consistently does not show Topoisomerase-II α (TOPO2A) gene amplification, either in the primary and in the lymph node metastases (95% of cases according to Brunello et al.), suggesting the rationale for the anthracyclines chemotherapy resistance. Indeed, TOPO2A gene amplification was shown to be a good predictor of response to anthracyclines (35).

Neoadjuvant setting

The meta-analysis of Petrelli et al. shows that lobular histology is associated with a three-fold lower chance of pathological complete response (pCR) and a two-fold lower possibility of breast conservation (36). Thus, in the context of ILC, neoadjuvant chemotherapy (NACT) does not achieve its two main goals, i.e. downsizing the primary tumor and increase the rate of BCS (37). Moreover, in the meta-analysis of 12 neoadjuvant trials performed by Cortazar et al., the achievement of a pCR was not a significant pre-requisite for a better event free survival (EFS) in ILC (38). According to the data reported by Cristofanilli et al., the difference in pCR rate between ILC and IDC persisted even after adjusting for HR status and the use of taxanes (1). The lower rate of pCR may probably be explained with the higher rate of HR positivity in ILC. In this regard, Buzdar et al. found that the rate of pCR are significantly higher in patients with HR negative tumors (1). The higher rate of mastectomies for ILC may be logically associated to the poorer response to chemotherapy, to the diffuse nature of the disease and the difficult to determine the exact extent of residual lesions by imaging. Taking together, the results of these trials suggest that the use of primary systemic therapy in women with ILC should be restricted to patients with inoperable disease or HR negative tumors. New strategies need to be explored to increase the therapeutic window of neoadjuvant chemotherapy for ILC.

Endocrine treatment may be considered an appropriate treatment for HR positive breast cancer regardless of histology, despite a lower or absent pCR rate (23). It should not forget that chemotherapy as well may work (despite the lower magnitude) in patients with HR positive breast cancer (37, 39). Thus, research is moving on to identify molecular predictors for pCR beyond the pure histology (40). In this regard, according to Loibl et al., those ILC which are considered ‘biologically aggressive’ (i.e. HR negative and undifferentiated tumor grading), achieved a pCR rate comparable to non ILC, especially in younger patients (41).

Adjuvant treatment

To the best of our knowledge, there are no ‘modern’ adjuvant trials prospectively randomizing ILC patients to any treatment or stratifying all breast cancer patients according to histology. Thus, the vast majority of information in this regard are provided by retrospective analyses alone. According to Korhonen et al., a differential effect of adjuvant therapy in general did not emerge between ILC and IDC (42).

Although treatment decision should be based on the classical prognostic and predictive factors as for IDC, women with lobular breast carcinoma are currently less frequently candidate to adjuvant chemotherapy, due to the perceived better prognosis. Indeed, evidences support the existence of subgroups of low risk ILC displaying an excellent prognosis even without adjuvant therapy (i.e. pT1pN0, low Ki67) (24). Moreover, in the study of Truin et al., adjuvant chemotherapy seems to do not confer any additional benefit in post-menopausal patients with pure or mixed type lobular breast cancer receiving hormonal therapy, with a 10-year survival rate of 68% after hormonal treatment alone, and 66.3% after hormonal therapy and chemotherapy (34). The authors explain the lack of sensitivity of ILC to chemotherapy with the inactivation of E-cadherin, which is thought to increase the transition of lobular carcinoma cells to mesenchymal cells, thus increasing the resistance to chemotherapy (43). The same trend is found in premenopausal patients, but the subgroup is too small to draw any conclusion. It is important to stress that mixed type ILC tend to respond in a similar way to chemotherapy as pure ILC. Deriving data from neoadjuvant setting, Colleoni et al. highlight the importance of a proper adjuvant endocrine treatment administered for a prolonged period of time (44).

As Katz et al. have previously suggested, there are insufficient evidence to support or withhold the use of chemotherapy in patients with ILC. Prospective clinical trial are needed to define the best treatment and prevention strategies (12).

Metastatic setting

To date, there are no validated evidences supporting the superiority of one therapeutic approach over any other for metastatic ILC. Neither NCCN guidelines, nor ESMO guidelines or the St. Gallen International Consensus Conference, considers lobular histology as a separate entity to IDC. In absence of any data, the choice should be accomplished according to the results emerged in metastatic IDC.

Future perspectives

Lobular breast carcinoma lacks of good proven standard medical therapies. HER2 gene is rarely amplified or the protein overexpressed, thus ruling out the use of trastuzumab. Moreover, TOPO2A is frequently not amplified, suggesting a higher chance of anthracyclines failure. There are also evidences indicating that the amplification or the overexpression of FGFR1 may be involved in the onset of endocrine therapy resistance. Therefore, the identification of novel therapeutic strategies in this subtype of breast cancer should be considered a clear medical need. As an example, given the higher rate of FGFR1 amplification, those drugs inter-
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Table 3 - Possible therapeutic target in ILC.

<table>
<thead>
<tr>
<th>Potential therapeutic</th>
<th>Targets</th>
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<tr>
<td>Topoisomerase II-α</td>
<td>KRAS</td>
</tr>
<tr>
<td>FGFR-1</td>
<td>NF1</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>AKT</td>
</tr>
<tr>
<td>Cycline D1</td>
<td>BRCA1</td>
</tr>
</tbody>
</table>

Cyclin D1, BRCA1, PIK3CA, AKT, FGFR-1, NF1, Topoisomerase II-α, KRAS, CDH-1 (E-cadherin-1 gene), CCND1, CDH-1 (E-cadherin-1 gene), CCND1, FGFR1, KRAS, NF1, AKT and BRCA1, which may represent other possible therapeutic target. In this regard, a series of potential therapeutic targets is listed in Table 3.

Conclusions

Lobular breast carcinoma represents a distinct entity of breast cancer with a peculiar morphology, molecular features, pattern of invasion, metastatic behavior and response to therapy. Nevertheless, treatment choices are derived from the benefit seen in the context of trials where the majority of patients are affected by invasive ductal carcinoma. However, emerging evidences suggest that this operative extrapolation might be not appropriate. Prospective evidences are needed to found the better therapeutic approach for these patients; in this regard, neoadjuvant studies may help to draw more rapid findings, while the conduction of adjuvant trials in this histology seem more complicated.

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