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Original Article

Adjuvant therapies for special types of breast cancer

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SUMMARY

Recent developments in the adjuvant treatment of breast cancer include an increasing attention to systemic therapies prescribed in homogeneous groups of patients according to the higher chance of benefit. A clear consequence of the current adjuvant treatment strategy is the importance of accurate and reliable histopathological assessment. A proper pathological evaluation may effectively support the definition of prognosis and treatment choice in niches of patients diagnosed with special types of breast cancer. Through the identification of special types of breast cancer, that account for up to 25% of all invasive breast carcinomas, it is possible to select patients with a very good prognosis often close to that of the general population (e.g. tubular and pure cribriform carcinoma). Other features, such as those related with invasive classical lobular carcinoma, might have important correlates of responsiveness to therapy other than indicators of outcome. It was in fact demonstrated that the response to primary chemotherapy is significantly lower in invasive lobular carcinoma, if compared with the ductal histotype. However, the use of available information on special types of breast cancer has been limited in tailoring adjuvant therapy, owing to the absence of standardized criteria and partial reproducibility for diagnosis. Moreover, due to the relative rarity of the disease a large number of features that identify for special types of breast carcinomas have today no particular correlation with the prognosis, and limited data are available on the biology of a large number of breast cancer subtypes. The development of more effective therapies for patients with special types of breast cancer requires tailored treatment investigations through international cooperation and should not rely on information predominantly contributed from small retrospective analyses. Examination of patterns of relapse and treatment response within subpopulations in multiple randomized trials is also mandatory to make progress and reach consensus on how to treat individual patients with special types of breast cancer.

Introduction

Care for patients with breast cancer tend to more selective interventions to minimize acute and late toxicity without compromising efficacy. In particular, appropriate adjuvant systemic therapy involves choosing treatments tailored to individual patients according to assessment of patient risk, comorbidities and preference.[1–3] A useful strategy to improve treatment effects is the identification of features, which are associated with response to therapy and outcome of the patients. Several classical risk factors that might select subgroup of patients with higher risk of relapse include nodal status, peritumoral vascular invasion, amplification or overexpression of HER2, high grade and/or high proliferation indexes.[4–7]

Moreover, recommended principles for the choice of therapies in operable breast cancer include the recognition of diverse subtypes of breast cancer and the identification of a set of targets based on genetic signature, molecular analyses and immunohistochemistry (e.g. predictive markers).[3] In fact, recent studies using DNA microarray profiling have led to the recognition that breast cancer is a heterogeneous entity at molecular and genetic level[8] and to the classification of different invasive breast cancer subgroups with common molecular features (luminal, Her-2, normal breast like and basal like).[8–12] Furthermore microarray based methods have led to the development of molecular taxonomy and of prognostic "gene signatures".[13–17]

Little attention has been dedicated to the identification of special types of breast cancer that displaying a distinct morphology might exhibit a distinct prognostic and predictive profile, if compared with invasive ductal carcinomas (IDC) of no special type or not otherwise specified (NOS).[18] IDC represent approximately 60–75% of all breast cancers and constitute a diagnosis of exclusion (e.g. a tumor that does not qualify for a special type) whereas breast cancer special types account for up to 25% of all breast cancers. According to the latest edition of the World Health Organization classification 17 distinct entities are recognized and include invasive lobular carcinoma, tubular carcinoma, invasive cribriform carcinoma,

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mucinous carcinoma and other tumors with abundant mucina, medullary carcinoma, metaplastic carcinomas, neuroendocrine tumors, apocrine carcinoma, adenoid cystic carcinoma, invasive papillary carcinoma, invasive micropapillary carcinoma, secretory carcinoma together with other less frequent types.[19]

Literature data indicate that the diagnosis of special types of breast cancer might be associated with a different outcome if compared with IDC with similar biological features and stages.[10] In particular, recognition of special types of invasive breast carcinoma allows for the identification of women with an extremely good prognosis. Consequently, an accurate and reliable histopathological assessment is crucial in order to detect these peculiar types of cancer as well as quantifies the target for adjuvant treatment.[18,20]

It is the intention of this report to discuss the evolving knowledge on special types of breast cancer in order to define reasonable treatment proposal within these patients.

Identification of novel target for therapy within special types of breast cancer

The category of "special histotypes" of breast cancer, identified by distinct morphological and cytological patterns, might represent a model for the study of breast cancer given their intrinsic homogeneity and the fact that each subgroup may be driven by a specific constellation of genetic and epigenetic events.[21] Although microarray studies have primarily analysed IDC and histological special types of breast cancer have not been systematically studied, the histopathological characteristics of these cancers may be correlated with distinct genetic changes, if compared with IDC of the same molecular subgroup, which might represent a possible target for future therapies.[21,22] For example, in metaplastic breast cancers a significant downregulation was observed for DNA repair pathways, including the BRCA1 DNA damage response pathway, PTEN, a gene possibly involved in the responsiveness to chemotherapy, as well as TOP2A, a molecular target correlated with the response to anthracyclines.[23–25] In addition, metaplastic cancers were found to show significantly higher expression of genes linked to myoepithelial differentiation if compared with IDC of basal-like phenotype.[23,25] On the other hand in medullary carcinomas an up-regulation of genes involved in immune response, including interleukins and IFN regulatory factors, as well as genes related to the apoptosis pathway was observed. Moreover, genes associated with cell invasiveness are downregulated, a factor possibly related with their favourable outcome.[21–26] Adenoid cystic carcinomas, which also display a basal-like phenotype but are characterized by favourable prognosis, display a low histological grade and downregulation of genes related to cell migration, proliferation and immune response.[21,22]

Invasive lobular carcinomas are characterized by markedly decrease or absence of E-cadherin immunophenotypical expression, if compared with invasive ductal carcinomas.[27] The CDH1 gene encodes this cell-cell adhesion molecule. Loss of function of E-cadherin pathway might contribute to the infiltrative and metastatic behaviors of breast cancer. Inactivation of E-cadherin through germline mutations in CDH1 and loss of heterozygosis has been also associated with a substantively increased risk of lobular carcinoma.[28,29] Finally, in classic lobular carcinomas recurrent amplifications on the FGFR1 locus were observed,[30,31] indicating FGFR1 as potential therapeutic target for a subgroup of lobular cancers.

Lobular carcinoma

Invasive lobular carcinoma (classic, alveolar, solid, plemorphic, tubulo-lobular) is the most common "special type" breast cancer. As a general rule, invasive breast cancers of low histological grade have been reported to have similar clinical presentations, immunohistochemical profiles and genome-wide transcriptomic patterns. Therefore it has been suggested that low-grade IDC and ILC and their respective precursors would form a "family" of lesions (e.g. low-grade breast neoplasia family).[32] Conversely recent reports provide evidence that ILC consist of diverse molecular subtypes and are transcriptionally distinct from histological grade subtype matched IDC, while classic and pleomorphic lobular carcinoma harbour similar patterns of genetic aberrations and may evolve along a common genetic pathway, despite the more aggressive nature of the latter.[33] Consequently, lobular carcinomas exhibiting small but relevant differences in the transcriptomic profiles metastatic pattern and clinical behaviour from IDC, warrant their separation as specific entities.[34]

Conflicting literature data are available on the outcome of ILC. On one hand some authors have concluded that ILC carries a poorer prognosis if compared to IDC[34,35] while others have found a similar outcome.[36–41] In particular, a large study focusing on 9,374 patients categorized as either pure IDC or ILC after central pathology review was recently published after a median follow-up time of 13 years.[42] There was a significant early advantage in disease-free survival and overall survival for the ILC cohort followed by a significant late advantage for the IDC cohort after 6 and 10 years, respectively. Similar patterns were observed in cohorts defined by ER status.[42] A second series comprises 301 consecutive 'classic' lobular breast carcinomas seen at one institution between 1994 and 2001, and compared to an equal number of matched invasive ductal carcinomas. Although there was no significant difference in disease-free or overall survival, the lobular group showed a trend to a delayed increased appearance of events (HR 1.27).[43]

A prognostic role of the histopathologic subtyping of ILC was hypothesized in the past years, with a possible more favorable outcome of the classic subtype of ILC (likely to be endocrine responsive, without HER-2 expression/gene amplification and usually categorized within the luminal A molecular subgroup), if compared with others, such as the alveolar, solid, and pleomorphic type. In particular in a study focusing on 530 patients with ILC, it was demonstrated a significantly increased breast-related events (hazards ratio of 1.80; 95% confidence interval, 0.04–3.10) and a trend toward reduced disease-free survival and overall survival, for the 'non classic' subtype compared with the classical type.[44]

It was recently showed that the response to primary chemotherapy is lower in terms of pCR (0–3%) in locally advanced invasive lobular carcinoma (ILC) compared with invasive ductal carcinoma (IDC), with a greater need for mastectomy for the former.[45–49] ILC is characterized by a significantly higher expression of steroid hormone receptors if compared with IDC, a possible circumstance that might contribute to the lower response to preoperative chemotherapy. These results indicate that a tailored approach should be considered in ILC, based upon proper adjuvant endocrine therapy administered for a prolonged period of time.

Luminal special types with favourable outcome

Within luminal breast cancer, several special types (luminal A molecular type) display an extremely good prognosis often approaching or equalling that of the general population.[50] In particular, pure tubular carcinoma is a rare histological carcinoma, correlated with a very favourable prognosis.[51–53] Current published data indicate that when compared with "grade 1" IDC, tubular carcinoma is associated with longer disease-free survival and breast cancer-specific survival close to normal life expectancy.[52] In particular in this study, none of the patients with TC developed distant metastasis. Analysis at transcriptional level suggests that TC and "grade 1" IDC are very similar, with small but significant differences between these two entities. An up-regulation of

"Estrogen Receptor Signalling Pathway" was observed in pure TC, which may account for the reported favourable prognosis of these tumors if compared with "grade 1" IDC.[53] The genomic similar cribriform carcinoma also correlates with excellent prognosis, irrespective of lymph node metastases.[53,54] Mucinous carcinoma, if present in pure form also predicts a 10-year survival of >90%.[21,22,55]

Within node negative disease special types of breast cancer were demonstrated to be significantly correlated with a favourable prognosis. In a study focusing on 767 node negative breast cancer patients, those with special types of invasive ductal carcinoma (including also mucinous, tubular, and papillary carcinomas) had a significantly higher recurrence-free survival rate than those with invasive ductal and lobular carcinomas.[56] These results indicate that for selected patients with favorable luminal special types no systemic therapy or endocrine therapy with the aim of prevention might be discussed.

Identification of special types within the triple negative subtype

Triple negative breast cancers represent about 15% of all breast cancers and are correlated with an adverse clinical course, with an increased likelihood of disease recurrence and death.[57] There is currently no specific targeted treatment for patients with triple-negative breast cancers, due to the paucity of data on which to base treatment selection.

On the other hand there is substantial evidence to support the need to further define distinct biological entities within triple negative breast cancer that require a differentiated approach to treatment and clinical trial investigation. In particular, medullary carcinoma requires a careful histological assessment. The diagnosis of this tumor is frequently accompanied by inter-observer low reproducibility despite of the availability of strict exclusively morphological criteria.[58] The identification of typical node-negative medullary carcinoma is crucial since it is related with a good prognosis regardless of histological grade.[59]

Within the context of triple negative breast cancer, adenoid cystic carcinoma of the breast also requires special attention,[60] due its favourable outcome although it does not express oestrogen receptor. In a similar way secretory carcinomas have indolent clinical behaviour and consistently display a triple negative and basal phenotype.[61]

Recognition of specific-type histology in estrogen receptor-negative breast carcinoma is essential in order to properly weigh the risks and benefits of all therapeutic options, including no adjuvant treatment in selected patients with co-morbities and favourable prognosis. In contrast, breast cancers presenting with areas of sarcoma, carcinosarcomas and/or metaplastic carcinomas still represent a challenge since little information is available about their clinical course.[62,63] Some Authors have suggested that these heterogeneous subgroups of triple negative tumors are linked to an adverse outcome although a great range of presentations is possible and classical factors such as grade might correlate with the prognosis.[64]

Other uncommon special types

A small amount of information is still available about the outcome of some uncommon special types of breast cancer. These include micropapillary carcinoma, a luminal B type tumor, defined by nest of cells with the classic inside out growth pattern, that has the prediction of a high likelihood of lymph node involvement.[65] A poorer prognosis if compared with IDC, was reported.[66] Genomic analyses suggest that it might represent a distinct molecular entity with specific genetics changes.

Pure apocrine carcinomas are characterized by epithelium with apocrine differentiation and, irrespective of grade, by a characteristic steroid-receptor expression profile (ER−, PGR−, AR+).[67] Recently published studies demonstrated that apocrine tumors are different from common luminal and basal cell subtypes and defined by a "molecular apocrine" gene expression profile.[68] Moreover, distinct expression of HER-2 and EGFR was observed in apocrine carcinomas. In fact, HER-2 overexpressing apocrine carcinomas were mostly negative for EGFR protein, while a majority of HER-2 negative cases (triple-negative apocrine carcinoma) over-expressed EGFR and could be classified as basal-like breast carcinoma. These findings may have significant therapeutic implications and might be associated with the patient's outcome.[69] Literature data indicate that pure apocrine (molecular apocrine phenotype) and apocrine-like carcinoma (luminal phenotype), display a prognosis similar to IDC, with an outcome influenced by the expression of biological features such as HER-2, EGFR and steroid hormone receptors (ER, PR, AR).[69]

Finally limited data, due to their absolute rarity, are available for several special types (lipid-rich carcinoma, oncocytic carcinoma, acinic-cell carcinoma, glycogen-rich clear cell carcinoma, sebaceous carcinoma).[70] In fact few cases have been reported in literature and consequently no definite conclusion on the outcome of patients with these tumors can be drawn.

Conclusions

Limited results are reported in the literature on the outcome of special types of breast cancer. Consequently restricted information from retrospective analyses on tailoring adjuvant treatment for an individual patient are available. However, results available in the literature indicate that patterns of relapse vary in different subpopulations and that consequently the pathologist has a crucial role for the selection of appropriate therapies.

Special types of breast cancer include a spectrum from patients at very low risk for whom there is little evidence supporting the use of endocrine therapy, to those with higher risk disease where combined adjuvant therapy appears clearly justified. It should be emphasized that the tumor categories at the present time identified are more than mere architectural patterns and include heterogeneous clusters of tumors. Therefore, the identification of further tumor subtypes amenable to targeted treatments represents a research priority.

Within luminal tumors, favorable histotypes (e.g. tubular, cribriform, mucinous, papillary) may be suitable for no therapy or endocrine therapy alone. On the other hand, treatment should be tailored according to tumor biology and disease extension for lobular and apocrine carcinomas, as for IDC. Finally, there is need to tailor the approach within the heterogeneous "triple-negative" subtype (e.g. adenoid cystic or medullary vs metaplastic carcinomas).

In order to improve therapeutic results, further retrospective analyses based on a reliable biological assessment of combination of prognostic and predictive factors (multivariate assessment) should be developed. In fact, data from past series include information on several aspects of the disease collected in the earlier period, when the various prognostic and predictive factors were not available in the fashion they are today. Moreover, no central pathology review was carried out in a significant proportion of published studies. Also, the development of tests that contain gene signatures specific for selected special types[71,72] may have additional valuable qualities.

In conclusion, the efficacy of adjuvant systemic therapy for early breast cancer depends on variable features, including those of the tumor, the patient, and the treatment itself. Within the context of special types, tailored treatment investigations and

examination of patterns of treatment response during the course of follow up within subpopulations in multiple randomized trials is required. Definition of specific niches for tailored research through international cooperation is key to make progress and solidify consensus on how to treat individual patients with special types of breast cancer.

Conflict of interest statement

The authors have no conflict of interest to declare.

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