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Original Article

Lessons on responsiveness to adjuvant systemic therapies learned from the neoadjuvant setting

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SUMMARY

Aims: Recommended principles for the choice of therapies in operable breast cancer include the recognition of diverse subtypes of breast cancer and, based on genetic signature and immunohistochemistry, the identification of targets and related factors predictive of response. We review recent developments in the knowledge of established predictive factors in the neo-adjuvant setting.

Methods and Results: Experimental and clinical studies have shown that the degree of expression of estrogen receptor (ER) and progesterone receptor (PgR) of the primary tumor defines distinct biological entities that require a differentiated approach to neoadjuvant treatment and clinical trial investigation. In particular, tumors that express high levels of both steroid hormone receptors in a majority of cells derive no or low benefit from preoperative chemotherapy, while the absence of expression of ER and PgR was significantly correlated with the probability of pathologic complete remission (pCR). It was also demonstrated that the pCR rate to primary chemotherapy is significantly lower in invasive lobular carcinoma, frequently characterized by a high expression of steroid hormone receptors, if compared with the ductal histotype. Direct or indirect measures of high cell proliferation (elevated Ki-67 labeling index and high grade) identified patients with tumors responsive to chemotherapy in the preoperative setting. These factors might therefore assist in the identification of patients who might benefit from chemotherapy, in particular those patients with endocrine responsiveness. HER2 overexpression or amplification represents a target for neoadjuvant treatment with the humanised monoclonal antibody against its extracellular domain, but is also a factor predictive of response to neoadjuvant systemic therapies. A statistically significant positive correlation between HER2 positivity and pCR rate in patients treated with neoadjuvant chemotherapy was recently shown.

Conclusions: Results from studies in the neoadjuvant setting indicate that the use of factors predictive of response may permit a more effective application of therapies identifying patients likely to obtain substantial benefit from treatment.

Introduction

A useful strategy to improve knowledge regarding treatment effects is the early identification of those features which are associated with response or resistance to therapy. Preoperative therapy might be advantageous for patients with breast cancer in several ways in addition to allowing breast conservation surgery in some of the patients. In fact, the response to the primary treatment may be used as a prognostic marker, since it has been demonstrated to be associated with a longer disease-free survival (DFS) compared with no-response. In particular the degree of response predicts overall outcome in terms of DFS.[1,2] It has in fact been assumed that pathological complete remission (pCR) is a valid surrogate of long term survival and cure from breast cancer. A large body of evidence from retrospective analyses of well conducted clinical trials supports this assumption.[1–4] However, several limitations concerning the predictive value of pCR still exist.

In fact, the definition of pCR varies in published studies and only recently has it been accepted that it should be defined as the absence of invasive cancer in both the primary breast tumor and axillary lymph nodes.[5] Moreover, pCR can be achieved only in a minority of patients. In particular, pCR rates range from 30% to 40% in those patients whose tumors express neither estrogen receptors (ER) nor progesterone receptors (PgR), whereas in patients with endocrine responsive tumors pCR rates range

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between 2% and 10%.[6–8] Therefore, more than 75% of the patients currently fail to achieve a pCR and have an increased risk of relapse and death, even if they have received additional systemic therapy. Limited data are available on factors able to predict prognosis of breast cancer after preoperative chemotherapy in patients who failed to achieve a pCR and who remain at substantial risk of relapse.

Conflicting results are reported in the literature on the value of factors predictive of response in the neoadjuvant setting. Potential limitations of available data include inadequate patient selection, different methods and cut-offs used in the various studies for the determination of selected prognostic factors (i.e. steroid hormone receptors, HR), different adjuvant strategies and heterogeneity of regimens used. Mature studies were designed in an era when neoadjuvant therapies were selected according to the stage of the disease and where factors predictive of response (i.e. HR expression for predicting response to endocrine therapies) were uncommonly taken into consideration. Breast cancer is now recognized as a heterogeneous disease in which the chance that one treatment program will benefit all is not realistic.[9] Finally, only a minority of published studies have been reported with a median follow-up exceeding 5 years, yet such prolonged follow-up is particularly important for the assessment of delayed events seen among patients with endocrine-responsive disease.[10]

Established biomarkers, apart from the degree of expression of HR already mentioned, that might have a predictive value in patients treated with preoperative therapy, include epidermal growth factor receptor 2 (HER2) gene expression, grade, histotype and markers of proliferation such as Ki-67 labeling index.[5]

Improved knowledge and application of traditional factors specifically involve steroid hormone receptors, HER2 and Ki-67 expression. Emerging experimental data suggest that ER and PgR expression and HER2 pathways are interactive.[11] Also, a correlation between type of preoperative therapy and predictive value of Ki-67 expression was recently reported.[12] To seek information on the predictive value of the expression of ER, PgR, Ki-67, HER2 expression either as single factor or combined, and their pertinence in the therapeutic neoadjuvant algorithm we review recent developments in the understanding of these established factors.

Steroid hormone receptors

There is substantial evidence to support the hypothesis that the degree of expression of HR of the primary tumor defines distinct biological entities that require a differentiated approach to treatment and clinical trial investigation.

The pCR rate was significantly higher following preoperative chemotherapy for patients with ER-negative tumors, compared with the receptor-positive cohort.[6–8] Despite the significantly higher incidence of pCR for patients with ER-negative disease, the 5-year DFS was significantly worse for this cohort compared with the positive expression cohort in retrospective analyses.[6–8] A different pattern of response and outcome to chemotherapy for ER-absent tumor versus both low and positive cohorts was reported,[8] supporting the hypothesis that receptor-absent breast cancer is a distinct entity from that with even low levels of receptor expression.[13]

In a recent study, the level of expression of ER and PgR was found to be significantly correlated with the probability of response and with the outcome of the patients.[14] No pCR was observed within the cohort of patients defined as highly endocrine-responsive (ER and PgR expressed in ≥50% of the cells) which compares with 3.3% of those with ER or PgR expressed in 0–49% of the cells (incompletely endocrine responsive) and 17.7 % of those with HR-absent (endocrine non-responsive) tumors ($p < 0.0001$). Moreover, the outcome of the patients in terms of 5-year DFS and OS was significantly better for the former cohort if compared with those patients with endocrine non-responsive tumors.

Also the presence of a specific histotype might be correlated with the probability of response and with the outcome of the patients. It was recently shown 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.[15–20] Conversely, the outcome of ILC appeared to be more favourable than for IDC.[15,20] ILC is characterized by significantly higher expression of steroid hormone receptors when compared with IDC, which might contribute to the lower response to preoperative chemotherapy.

On the other hand, neoadjuvant endocrine therapy in endocrine-responsive disease is safe, being associated with a very low incidence of tumour progression, and is able to induce a high rate of objective remissions. There is however a small body of evidence regarding neoadjuvant endocrine therapy. Preoperative endocrine therapy has in fact been historically restricted to postmenopausal women and randomized trials have been conducted in this patient setting.[21,22] Results from two large randomized trials focusing on neoadjuvant endocrine therapy in postmenopausal patients with endocrine responsive disease, support the hypothesis of a correlation between the probability of response and the degree of endocrine responsiveness. In particular, there were statistically significantly more responders with higher ER levels in both studies.[21,22] Moreover, there was a positive significant correlation between ER level and degree of Ki-67 suppression for patients at both 2 and 12 weeks of endocrine treatment.[23] These results support a role for endocrine therapy in those patients who presented distinct features of response (i.e. high expression of HR) to endocrine treatments.

Markers of proliferation

Tumor proliferation fraction is an important predictor of prognosis. Ki-67 is an antigen present in all phases of the cell cycle except G_0,[24] and Ki-67 labelling index (LI) is a measure of tumor proliferation that has been correlated with outcome in several studies[24,25] and in a recent meta-analysis conducted in more than 12,000 patients.[26]

The presence of elevated Ki-67 has been found to predict response to chemotherapy in locally advanced breast cancer. In several retrospective analyses conducted on a large number of patients, both clinical response and pCR were significantly higher in those patients whose tumors presented a high Ki-67 LI, although different cut-offs were used.[27–30] Conversely, no statistically significant relationship between baseline Ki-67 and response to neoadjuvant treatment has been reported for endocrine therapy.[21,22]

More recently, a study focusing on 228 postmenopausal women with endocrine responsive breast cancers treated within a neoadjuvant endocrine therapy trial, showed, at the multivariable analysis of post-treatment tumor characteristics, that Ki-67 expression was independently associated with both RFS and BCSS.[31] In particular a low Ki-67 expression after neoadjuvant endocrine therapy was found to significantly correlate with improved outcome.

The results of the this study indicate that measures of tumour cell proliferation such as Ki-67 expression could potentially identify patients who require further therapy (adjuvant chemotherapy as well as endocrine therapy) after preoperative endocrine therapy in locally advanced breast cancer. A similar prognostic role for Ki-67 at final surgery have been reported after preoperative chemotherapy in several studies.[12,32]

HER2 expression

Conflicting data are available on the relationship between HER2 expression and response to preoperative chemotherapy. This

might be explained by the small sample sizes, heterogeneity of examinations, methods, and cut-offs used in the various studies. A recently published trial on a large number of patients showed a statistically significant positive correlation between HER2 positivity (defined as 3+ with immunohistochemistry), HR-negativity and pCR rate.[33] A significantly higher probability of pCR was observed in HER2-positive tumors both in the population with ER-positive and that with ER-negative tumors. A second study recently confirmed that patients whose tumors overexpress HER2 have a higher probability of pCR if compared with the HER2-negative cohort irrespective of ER expression.[34] This study showed also that the achievement of pCR significantly correlated with improved RFS in patients with HER2-positive disease as well as in those with HER2-negative tumors.

The probability of relapse was reported to be significantly higher for the population that overexpressed HER2 if compared with HER2-negative tumors in 2 large studies on preoperative chemotherapy.[33,35] In particular, in a retrospective analysis including 1,731 patients, progression-free survival rates were significantly worse for HER2-positive disease both in the HR-positive and HR-negative cohorts of patients.[34] These results support a possible role for chemotherapy in the population with HER2 positive disease.

Discussion

Historically, neoadjuvant chemotherapy has been administered almost universally to patients with large tumors with the few exceptions of small series of elderly women for whom an endocrine preoperative therapy seemed to be the only treatment which could be proposed.[36] Therefore the bulk of information available is much larger for chemotherapy if compared with neoadjuvant endocrine therapy and with targeted treatments that have been only recently introduced.

Steroid hormone receptor status is one of the strongest predictive markers for neo-adjuvant therapy. Available results suggest a different pattern of outcome according to the degree of potential endocrine responsiveness. Recent unplanned retrospective analyses provide substantial additional evidence to support the hypothesis that the degree of expression of steroid hormone receptor status of the primary tumor defines distinct biological entities that require a differentiated approach to treatment and clinical trial investigation. In particular, on the one extreme, highly endocrine responsive tumors or selected endocrine-responsive histotype (ILC) might be suitable for endocrine therapy alone in particular if low risk factors are present; on the other extreme, patients with ER- and PgR-absent tumors should be approached with chemotherapy, combined with targeted therapy if necessary.

A complex interrelationship between known (and unknown) features in patients with some endocrine responsiveness exists and if factors predictive of chemotherapy responsiveness are present (i.e., overexpression of HER2, high Ki-67, high grade), chemotherapy may be required and added to endocrine therapy. However, non-endocrine, incompletely endocrine and endocrine responsive tumors represent heterogeneous groups of disease where the identification of distinct clinical entities is the key achievement for future trials. Different approaches can be used in order to improve our understanding of those factors that might predict a response to targeted treatment.

On one hand, further retrospective analyses based on a reliable biological assessment of a combination of predictive factors (multivariate assessment) should be developed. Limited data are available on the combination of factors which are predictive of prognosis of breast cancer in patients candidated for preoperative therapy, although several models or nomograms were presented in the past based on both clinical and pathological features.[36–38] 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 as they are today.[39] Moreover, no central pathology review was carried out in some of these studies.[36] The development of models or nomograms which might be able to predict response and outcome based upon expression of both classical and newer features of the primary tumor is a priority.

On the other hand, tests that contain signatures for proliferation, ER and ER regulated genes, such as the 21 gene Recurrence Score™[40] or the MammaPrint™[41] may have additional predictive value. In particular, advantages include a possible more precise evaluation of selected features (ie., ER expression), as measured by the Onco*type* DX assay™, with quantitative RT-PCR if compared with IHC and biochemical assay,[42] and central laboratory testing. Genetic testing on breast tumors has already identified distinct subtypes of breast carcinomas that are associated with different responses to chemotherapy and with different clinical outcomes in the preoperative setting.[43] Recently, a correlation between the probabilities of pCR as a function of gene expression such as the 21 gene Recurrence Score was reported.[44] However, gene expression profiling still remains inadequate today in the identification of the population which can avoid preoperative chemotherapy or who are candidates for a very high probability of pCR.[39] This might be related to methodology issues as the large number of variables (genes) to be analyzed in relatively small data sets and the facts that gene lists of those patients who respond to the treatment might be subject to classical predictive factors (i.e., ER) associated genes.

In conclusion, lessons from the neoadjuvant setting are far from being perfect with major issues of controversy still to be resolved. The definition of specific niches for tailored research is a priority and improved selection and combination of predictive factors and predictive tools is of key importance for future trials.

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