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Viewpoints and debate

Neoadjuvant treatment of HER2 and hormone-receptor positive breast cancer – Moving beyond pathological complete response

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ABSTRACT

Pathologic complete response (pCR) was noted to be prognostic in all but hormone receptor-positive (HR) breast cancer cases even when HER2 is overexpressed. Evocative data suggest that HER2-positive breast cancer patients are a heterogeneous population and a subset of HER2-positive and HR-positive tumors biologically behave more like HER2-negative. Identification and targeted monitoring of these patients is crucial to consolidate data aiming to optimize combination treatment with new agents, thereby avoiding overtreatment with chemotherapy. The questions surrounding HER2-positive and HR-positive breast cancer patients treatment as well as the potential direction towards development of surrogate markers alternative to pCR are discussed.

Introduction

Neoadjuvant trials are a new and reliable approach to testing new agents for breast cancer (BC). Aside from the clinical benefit derived by tumor downstaging, neoadjuvant therapy may provide in fact valuable prognostic information, considering that patients achieving pathologic complete response (pCR) show improved long-term outcome as compared to those left with residual disease after neoadjuvant systemic therapy. Based on this evidence, the FDA recently released specific guidelines to use pCR as a surrogate endpoint to support accelerated drug approval for BC neoadjuvant treatment [1]. To date, however, there has not been a uniform definition of pCR, which has made reporting and interpretation of data from neoadjuvant trials challenging. The FDA has proposed the following definition for regulatory purposes: pCR is defined as the absence of any residual invasive cancer on hematoxylin and eosin evaluation of the resected breast specimen and all sampled ipsilateral lymph nodes following completion of neoadjuvant systemic therapy. Adoption of a single term with a standard definition would facilitate discussion of proposed trial designs and interpretation of clinical trial data to support accelerated approval. Importantly, according to FDA, the definition of pCR proposed in their guidance would have the greatest likelihood of predicting clinical benefit for regulatory purposes in patients with early-stage breast cancer who achieve pCR following neoadjuvant systemic therapy. However, pCR rates significantly vary depending on BC subtypes, ranging from 8.3% in hormone receptor-positive (HR-positive) to 31.1% in triple negative cases, with aggressive subtypes more highly associated with event-free survival than smaller, less aggressive tumors [2]. In patients with HER2 overexpressing (HER2-positive) BC, trastuzumab dramatically changed the disease's natural history and improved outcome [3,4]. However, pCR rates of neoadjuvant trastuzumab-containing regimes are still in the range of 30–60% with 3-year relapse-free survival (RFS) of 71–78% [5], clearly showing that a substantial number of HER2-positive BC patients undergoing surgery still present residual disease notwithstanding prior neoadjuvant therapy.

Significance of pCR in HER2-positive and HR-positive tumors

Growing evidence indicates that response to anti-HER2 agents and the prognostic impact of pCR after anti-HER2-based therapy depend on HR status. In the retrospective study by Guarneri et al., pCR rates among patients with HER2-positive BC treated with anthracycline/taxane-based chemotherapy was 15% and 29%

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($p < 0.001$) in HR-positive and HR-negative cases, respectively [6]. The addition of trastuzumab produced similar differences according to HR status, with pCR rates 1.5–2 fold lower in HR-positive than in -negative cases [6]. More recently, data from the NeoSphere [7], NeoALTTO [8] and TBCRC006 [9] trials further confirmed these findings, consistently showing that pCR rates were significantly lower in HR-positive than HR-negative tumors, regardless the type of HER2-targeted therapy with single or combined HER2 blockade (Table 1) [7–19]. Therefore, new neoadjuvant strategies are urgently needed to increase pCR rates and to improve clinical outcome of HER2-positive/HR-positive BC patients.

Nevertheless, the significance of pCR in this subset of patients needs further considerations. The pooled analysis of the German neoadjuvant studies reported that pCR is a suitable surrogate endpoint for HER2-positive/HR-negative but not for HER2-positive/HR-positive BC patients [20]. Indeed, pCR in HER2-positive/HR-positive cases was relatively uncommon (11%–22%), even with the use of trastuzumab, and achievement of pCR in this subgroup was not prognostic for survival. Although the reasons for these findings are not entirely clear, a possible explanation is that lack of pCR to chemotherapy in less proliferative HR-positive tumors predicts greater benefit to future hormonotherapy. Thus patients with HER2-positive/HR-positive BC not achieving a pCR are not necessarily at poor prognosis, as adjuvant hormonotherapy may further improve clinical outcome. It is important to note, however, that among patients with pCR, those initially diagnosed with HER2-positive/HR-positive BC tend to report the lowest 5-year disease-free survival (DFS) as if, when present, pCR in HER2-positive/HR-positive cases is less beneficial. Although no analysis on biological and clinical characteristics of these patients relapsing after pCR has been done, it is likely that the poorer outcome in this subgroup is due to either decreased benefit from adjuvant therapy or rapid onset of molecular resistance to anti-HER2 agents and/or hormonotherapy. In support of this hypothesis, evidence exists that relapses after pCR generally occur in young patients and/or in patients with locally advanced BC at presentation [21]. Therefore, in patients with HER2-positive/HR-positive, pCR is infrequent and when reported it does not yield the same good outcome as compared to the rest of patients treated with trastuzumab-based neoadjuvant regimens. Data from adjuvant studies further confirm these findings [22]. In the HERA trial, the hazard ratio for DFS among patients with HER2-positive/HR-positive early BC had the widest confidence intervals as compared with the other subtypes. Although the limitations of the *post-hoc* analysis permit no definitive conclusion on the differential effect of adjuvant trastuzumab according to BC subtypes, these data demonstrate that HER2-positive BC patients are a heterogeneous population. The identification and characterization of the HER2-positive/HR-positive BC subset is essential to avoid overtreatment especially in patients with small tumors, who may benefit from hormonotherapy alone or combined with a HER2 targeted therapy without chemotherapy. Indeed, a crosstalk between the HR and HER2 pathways exists, which plays a major role in the development of both intrinsic and acquired resistance to endocrine agents. Emerging data suggests that this crosstalk is bidirectional and is involved in resistance to HER2-directed agents [23]. Therefore, targeting both HR and HER2 pathways may be beneficial in overcoming resistance to endocrine and anti-HER therapies and optimize clinical outcome.

Table 1
Pathological complete response (pCR)[a] rate according to hormone-receptor (HR) status in neoadjuvant trials with anti-HER2 agents.

Study [Ref] phase		No. of patients	Clinical stage	Neoadjuvant regimen	pCR rate	*p*	pCR rate HR-positive	pCR rate HR-negative
Randomized trials with trastuzumab	MD Anderson [10]	42	II–III	P → FEC	26%	0.016	27.2%	25%
	Phase III			P + T → FEC + T	65%		61.5%	70%
	NOAH [11]	235	III	AP → P → CMF	19%	0.001	17%	22%
	Phase III			AP + T → P + T → CMF + T	38%		18%	48%
	ABCSG-24 [12]	90	II–III	EC ± Cap	26% (breast only)	0.369	NR	NR
	Phase III			EC ± Cap + T	40% (breast only)			
	REMAGUS 02 [13]	120	II–III	EC → D	19%	NR	20.5%	19%
	Phase II			EC → D + T	26%		20.5%	32%
	H2269s [14]	30	II–III	D + CBDCA	7.1% (breast only)	0.0801	NR	NR
	Phase II			D + CBDCA + T	40% (breast only)			
Randomized trials comparing HER2-targeting approaches	NeoALTTO [8]	455	II–III	Weekly P + T	28%	0.0007[b]	22.7%	36.5%
	Phase III			Weekly P + L	20%		16.1%	33.7%
				Weekly P + T + L	47%		41.6%	61.3%
	NeoSphere [7]	417	II–III	D + T	23%	0.0141[b]	20%	36.8%
	Phase III			D + Pert	17%		17.4%	30%
				D + Pert + T	42%		26%	63.2%
				Pert + T	12%		5.9%	27.3%
	NSABP B-41 [15]	519	II–III	AC → weekly P + T	49.4%	0.056[b]	46.7%	65.5%
	Phase III			AC → weekly P + L	47.4%		48%	60.6%
				AC → weekly P + T + L	60.2%		55.6%	73%
	GeparQuinto [16]	615	II–III	EC + T → D + T	44%	0.04	NR	NR
	Phase III			EC + L → D + L	30%			
	CHERLOB [17]	121	II–III	P + T → FEC + T	25%	0.019[b]	25%	26.6%
	Phase II			P + L → FEC + L	26.3%		22.7%	35.7%
				P + T + L → FEC + T + L	46.7%		35.7%	56.2%
	GEICAM 2006–14 [18]	99	II–III	EC → D + T	48%	0.01	NR	NR
	Phase II			EC → D + L	24%			
	Holmes et al. [19]	100	II–III	FEC → weekly P + T	54%	NR	NR	NR
	Phase II			FEC → weekly P + L	45%			
				FEC → weekly P + T + L	74%			

A = doxorubicin; Cap = capecitabine; CBDCA = carboplatin; CMF = cyclophosphamide, methotrexate, 5-fluorouracil; *D* = docetaxel; *E* = epirubicin; FEC = 5-fluorouracil, epirubicin, and cyclophosphamide; L = lapatinib; NR = not reported; P = paclitaxel; Pert = pertuzumab; T = trastuzumab.

[a] pCR = defined as no invasive tumor in the breast and axilla, if not otherwise specified.

[b] Comparison between dual HER2-targeted therapy + chemotherapy versus trastuzumab + chemotherapy.

Table 2
Summary of studies assessing biomarkers in HER2 positive breast cancer.

Biological markers		Type of study [Ref]	Patient population (*n*)	Results	Conclusion/remarks
Proteins	Basal p95/HER2	Retrospective [37]	MBC (93)	Decreased PFS (HR 1.9; $p = 0.017$) and OS (HR 2.2; $p = 0.012$) as compared with p95/HER2 negative	p95/HER2 is a marker of poor prognosis (TBC in RCT)
		Analysis from RCT [38,17]	NeoAdj (153) NeoAdj (88)	pCR 58.2% *vs* 32.6% in p95/HER2-negative *vs* positive pts (0.009) in the GeparQuattro study No difference in the CHERLOB study	Inconclusive data on p95/HER2 predictive value
	Basal Ki67	Analysis from RCT [39]	NeoAdj (1166)	Ki67 significantly linked to prognosis in uni- and multivariate analysis Ki67 $\leq$ 15% *vs* 15.1%–35% *vs* > 35% had pCR% of 4.2%, 12.8%, and 29.0% ($p < 0.0005$)	Ki67 is associated with poor prognosis and increased pCR (TBC in RCT)
	Post-therapy Ki67	Retrospective [28,40]	NeoAdj (102) NeoAdj (64)	High Ki67 expression correlated with poor DFS and OS Multivariate analysis showed Ki67 significantly ($p = 0.05$) associated with prognosis	Prognostic value of post treatment Ki67 to be further investigated
	Basal and post-therapy TOPOIIα	Retrospective [41]	NeoAdj (283)	Decreased DFS ($p = 0.010$) and OS ($p < 0.001$) in TOPOIIα cases Significant prognostic value of post-treatment TOPOIIα ($p = 0.002$)	Prognostic value of TOPOIIα to be further investigated
	Loss of PTEN and p110 expression	Retrospective [42]	MBC, EBC (155)	Decreased PFS correlated with basal expression of p110α ($p = 0.024$)	Prognostic value of PI3K activation to be further investigated
Immunological-related	FcYR	Retrospective [34]	MBC, EBC (54)	158 V/V genotype correlated with ORR (HR, 8.7; $p = 0$ 0.02) and PFS (HR 5.3; $p = 0.005$)	FcYR-mediated ADCC to be further investigated
	Lymphocyte Infiltration	Retrospective [32] Retrospective [43]	NeoAdj [25] EBC (1250)	Higher infiltration of CD8+ T cells, FOXP3(+) regulatory T cells (Tregs) and CD8(+) cytotoxic T lymphocytes as compared to HER2 negative cases ($p < 0.005$)	Value of reduced tumor-related immune suppression to be further investigated
Geneprofile	Blueprint PAM50	Retrospective [31] Retrospective [30]	NeoAdj (996) NeoAdj (437)	Increased predictive accuracy for pCR by adding the immune module to clinicopathologic characteristics (IDI, 0.093; $p = 0.004$) 40% of HER2-positive cases are luminal-type by BluePrint and present low response rates to therapy	Immune module scores and molecular subtyping improve estimation of pCR (to be further investigated)
		Prospective [44]	MBC [19]	High expression of 17q12-21 amplicon genes *HER2* and *GRB7* correlated with response to treatment ($p = 0.0015$)	PAM50-enriched profile associated with clinical benefit (to be further investigated)
Functional pathway	*PI3KCA*	Retrospective [36]	NeoAdj [46]	Alterations of PI3K genes are more frequent in HER2 positive cases without HER2 amplification ($p = 0.009$)	PTEN loss and *PIK3CA* mutations confer worse outcome and resistance to trastuzumab (TBC in RCT)
		Retrospective [45] Rettrospective [46]	NeoAdj, EBC, MBC (1889) NeoAdj (80)	PTEN loss correlated with poorer efficacy of trastuzumab (RR = 0.682, 95% CI: 0.550–0.846, $p = 0.000$) *PIK3CA* mutations correlated to decreased DFS ($p = 0.0013$)	
Metabolic profile	^{18}FDG PET	Analysis from RCT [47]	NeoAdj (86)	pCR rates twice as high for ^{18}FDG PET responders than non-responders (44% *vs* 19%, $p = 0.05$)	Metabolic responders have increased likelihood of pCR (to be further investigated)
Soluble	Circulating Tumor Cells	Prospective [48]	EBC (88)	CTCs are related to reduced DFS ($p < 0.023$) and OS ($p < 0.04$)	CTCs predict poor clinical outcome (to be further investigated)
		Retrospective [49]	MBC (53)	CTC count is a significant predictive factor for OS ($p < 0.01$)	
	Circulating Endothelial Cells	Retrospective [50]	NeoAdj (53)	Low baseline CEC associated with pCR ($p = 0.046$)	Value of CEC to be assessed in extensive studies
		Retrospective [51]	MBC [52]	Clinical responses correlated with low CEC ($p = 0.023$)	
	HER2	Review [52]	MBC, EBC	No clear correlation with response to treatment or OS	Prospective trials to investigate the clinical use of HER2 ECD test are needed

DFS = Disease Free Survival; EBC = early breast cancer; ECD = extracellular domain; ^{18}FDG PET = 18-Fluoro-deoxyglucose positron emission tomography; HR = hazard ratio; Integrated discrimination index (IDI); MBC = metastatic breast cancer; NeoAdj = neoadjuvant; ORR = overall response rate; OS = Overall Survival; pCR = pathological complete response, defined as no invasive tumor in the breast and axilla, if not otherwise specified; PFS = Progression free survival; RCT = randomized controlled trial; RR = relative risk; TBC = to be confirmed; *vs* = versus.

Searching for new surrogate markers to predict long-term clinical outcome from neoadjuvant therapies

Understanding which patients are eligible for new treatments is critical, especially in the neoadjuvant setting, where the lack of prognostic value of pCR makes the identification of alternative markers a priority for cancer research. The proliferation index Ki67 is a feasible marker widely studied as surrogate of disease relapse in patients undergoing neoadjuvant hormonotherapy. Results from a randomized trial comparing tamoxifen versus anastrozole, showed that differences in Ki67 suppression after 2 and 12 weeks of treatment mirrored those in RFS in companion adjuvant trials [24]. Further evidence for the importance of Ki67 suppression were provided by higher 2-week values of Ki67 predicting a significantly worse RFS [25]. However as HER2 positive tumors show poor reduction in Ki67 upon treatment with aromatase inhibitors, this marker may be of limited utility when used in the setting of neoadjuvant hormonotherapy [26]. Nevertheless, in BC patients receiving neoadjuvant chemotherapy, basal Ki67 values predict treatment response and prognosis, as the higher the basal Ki67 the higher the pCR rate and RFS [27]; and, even more importantly, Ki67 values after treatment predict prognosis in patients not achieving a pCR [28]. The use of Ki67 as a guide for neoadjuvant treatment has been the focus of the Z1031B study [29]. All patients enrolled in this study were initially treated with hormonotherapy during 2–4 weeks. A tumor biopsy was performed thereafter and, according to the Ki67 results, patients who had tumors with a high proliferation rate were recommended to switch to chemotherapy/surgery. The study reported a pCR rate of 6% among those patients who switched to neoadjuvant chemotherapy, which did not meet the study's predefined criteria for adequate activity. Nevertheless, the value of Ki67 in HER2-positve/HR-positive BC continues to be investigated in different trials with anti-HER2 targeted agents ± hormonotherapy, i.e. NeoPhoebe, PAMELA, PERELISA, with the ultimate goal of finding a valid strategy for patients unlikely to benefit from chemotherapy. In addition, clinical trials have already started to evaluate the utility of using molecular profiles for breast cancer management in the preoperative setting. Among these, the I -SPY I study tested the MammaPrint and the BluePrint 80-gene expression profiles to stratify response to neoadjuvant therapy according to molecular subtypes. In detail, the pCR rate was 5% in the luminal-A and 10% in luminal-B, 39% in HER2-type and 33% in the basal-like subtypes. These data support the use of Mammaprint and BluePrint to define the clinical correlation between molecular subtyping and treatment outcomes [30]. Furthermore, the pooled analysis, focusing on the associations between pCR and gene modules to discover biologically relevant and potentially druggable subtype-specific oncogenic pathways, showed a strong link between immune modules and pCR in HER2-positive tumors [31]. Both HER2 and estrogens have immunomodulatory effects on BC development by increasing intratumoral TRegs levels [32] and immunomodulation is a critical factor for trastuzumab antitumoral activity. Several studies have shown that in BC patients treated with trastuzumab-based therapy [33] the antibody-dependent cell-mediated cytotoxicity (ADCC) and the FcγR polymorphisms can reliably predict clinical response [34]. Enhancing antitumor immunity may therefore increase therapy efficacy in HER2-positive/HR-positive BC, a strategy that deserve further investigations in clinical trials. Finally, sequencing analysis in BC reported that dysregulation of the PI3K pathway is associated with poor response to HER2-targeted therapy [35]. Furthermore, alterations in the PI3K and HR signaling are prognostic for patient outcome in the HR-positive BC subset [36]. The crosstalk between PI3K and HR pathways is involved in resistance to chemotherapy with trastuzumab, thus leading to the conclusion that HR status influenced the prognostic significance of genomic alterations in HER2-positive tumors. If these data will be further confirmed, mutation analysis of PI3K status should become part of the routine biomarkers panel as it may be helpful in selecting the proper treatment of patients with HER2-positive/HR-positive tumors. Studies assessing biomarkers in HER2 positive breast cancer are summarized in Table 2 [17,28,30–32,34,36–52].

Conclusions

The addition of trastuzumab to neoadjuvant chemotherapy regimen significantly increases the pCR rates in all HER2-positive tumors. However, the benefit of trastuzumab is highest in HR-negative tumors and progressively decreases with increase in tumor HR expression. This information prompts the search of new strategies and/or new combination of therapies associated to an increased pCR but also novel surrogate markers of long-term outcome. Studies using surrogate markers as Ki67 and gene amplification and/or mutation are currently ongoing and promise to assist not only the choice of best neoadjuvant therapeutical approach but also to address the clinician in scheduling the proper treatment in the adjuvant setting in the next future.

Conflict of interest

Serena Di Cosimo is member of the speakers' bureau for GlaxoSmithKline S.p.A. and is a Consultant for TEVA pharmaceuticals. Grazia Arpino is member of the speakers' bureau for Roche S.p.A. and GlaxoSmithKline S.p.A. Daniele Generali has no conflict of interest to declare.

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