Review Article

Neoadjuvant therapy for locally advanced breast cancer: Focus on chemotherapy and biological targeted treatments' armamentarium

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ABSTRACT Despite progress achieved in diagnosis and therapy in recent years, locally advanced breast cancer (LABC) remains a major clinical issue. Biological characteristics and clinical behavior varies widely, ranging from indolent to locally aggressive or generalized disease. In depth knowledge of biology of cancer progression and cancer could lead to the identification of tumor characteristics associated with outcome. Neoadjuvant chemotherapy (NCT) integrated into a multimodality program is nowadays the established treatment in LABC. Although our efforts in this research task are ongoing, of special clinical interest is the integration of anti-HER2 and other biological therapies, as anti-angiogenesis targeted treatments, that may further improve the long term control of LABC. Clinical management of LABC could be modified based on molecular biology and an approach tailored to each patient will optimize therapy.

Key Words: locally advanced breast cancer; multimodality approach; neoadjuvant chemotherapy; biological therapy

J Thorac Dis 2010; 2: 160-170. DOI: 10.3978/j.issn.2072-1439.2010.02.03.8

Introduction

LABC refers to a term that includes a heterogeneous group of diseases. A subset of stage IIB (T3N0), stage III disease and inflammatory breast cancer (IBC) are included in this group (1). Data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program indicated that approximately 7% of breast cancer patients have stage III disease at diagnosis. Median survival time is 4.9 years, while the 5-year relative survival rate for this group of women is 55% when treated with multimodality treatment not including biologics (2).

Tumor size, lymph node involvement and the presence of inflammatory carcinoma are the main prognostic factors, while the prognostic value of tumor grade, ER/PgR and HER-2/neu status is not fully clarified (3-6). In addition, pathologic complete response (pCR) has emerged as the most commonly used surrogate endpoint and seems to be associated with a favorable prognosis (7,8).

In this selected group of patients improving overall (OS) and disease free survival (DFS) are major goals. The conversion of an initially inoperable breast cancer to an operable one or even more to conservatively operable is also of crucial importance. Nevertheless, both the locoregional and systemic control represent major clinical problems in LABC. The risk of recurrence and death is extremely high, particularly in poorly responding to induction chemotherapy patients (9,10).

Neo-adjuvant systemic therapy integrated into a multimodality program is the established treatment in LABC (11,12). Primary systemic over adjuvant therapy has the advantages of early initiation of systemic treatment; opportunity of drugs' delivery through intact vasculature; *in vivo* assessment of response to therapy; reduction of microscopic neoplastic dissemination during surgical procedures and a less extensive operation. On the contrary, NCT disadvantages are initial tumor size and number of involved nodes could not be accurately assessed; much greater disease burden to treat; uncertainty that neoadjuvant treatment will be beneficial with consequences of delay in curative local therapy; suspicion that it could promote drug resistance and increased risks for surgical complications (12-14).

Systemic neoadjuvant chemotherapy:

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No potential conflict of interest.

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Submitted Aug 18, 2010. Accepted for publication Sep 07, 2010.
Available at www.jthoracdis.com

ISSN: 2072-1439

evolution, major dilemmas and points of interest

History and early trials

The first prospective study for NCT in locally advanced, inoperable breast cancer is dated in 1973, by the European Institute of Oncology and the primary purpose was to downstage the primary tumor in order to achieve surgical resection (15). Many other trials followed in the past two decades studying the role of induction chemotherapy. Currently NCT followed by surgery, is the treatment of choice for patients with IBC or LABC (16,17). Recently this approach was also recommended for primary operable disease (18).

The early 80's and 90's trials that evaluated the role of NCT highlighted the potential of this treatment approach. These trials concluded survival improvement up to 25% at 10 years of follow up. These studies focused on anthracycline based or CMF [Cyclophosphamide- Methotrexate- 5-fluorouracil (5-FU)]-like regimens, compared with historical experience on local therapy alone. However, early trials were highly heterogeneous in many aspects. In fact, they included heterogeneous populations in regard with the stage of the disease. They usually included advanced together with earlier stages of operable breast cancer (OBC). They mostly used CMF-like and anthracycline containing regimens but also radiotherapy (RT) and rarely endocrine therapy. In addition, differences in defining operability especially in the 80's rendered even more difficult the comparison of groups studied with historical controls. Moreover, the majority of these studies were of small size, mostly non-randomized and did not report the long-term impact of the neoadjuvant approach on multiple outcomes, including survival. As a result, while highlighting the potential of induction chemotherapy in the treatment of breast cancer, these studies illustrated many of the difficulties associated with the evaluation of NCT benefits.

Despite multiple discrepancies, these early trials established a solid background for the development of randomized studies. This allowed a better determination of the long-term impact of this treatment approach and its relative benefit compared with adjuvant therapy. Consequently, we will attempt to address and present important questions and points of interest in the neoadjuvant treatment research in LABC, based on results from well established randomized trials and also with referral to this early pool of data.

Neoadjuvant vs adjuvant systemic chemotherapy

One of the early concerns has been the validation of NCT against adjuvant systemic therapy. Data in locally advanced disease are limited mainly due to the lack of randomized trials comparing neoadjuvant to adjuvant chemotherapy. In part this happened because many surgeons consider these tumors inoperable prior to chemotherapy. Contrarily, there is a large body of randomized trials in OBC. In these studies a minority of women with LABC is also enrolled.

In fact, two large randomized trials of National Surgical Adjuvant Breast and Bowel Project (NSABP) addressed the question of neoadjuvant versus (*vs*) adjuvant chemotherapy but both in OBC patients. In the NSABP B-18 trial (19), 1,523 women with primary OBC were randomly assigned to four cycles of doxorubicin (A) and cyclophosphamide (C) either prior or following surgery. No significant difference in OS among the two groups was noted, with a median follow-up of 9 years. However, women achieving a pCR had a 50% reduction in risk of death compared to the entire group. The larger NSABP B-27 trial (20), with 2,411 patients, evaluated the addition of a taxane following AC either in neoadjuvant or adjuvant setting in a three arm design: a) AC and then surgery, b) AC plus taxane and then surgery, c) AC, surgery and then adjuvant chemotherapy with a taxane. The addition of docetaxel (DOC) pre- or post- surgery also made no significant difference. Despite the fact that the pCR rate was almost doubled from 13.7% in the NSABP B-18, to 26.1% in B-27, a significant OS difference was not observed between the treatment arms. However patients with pCR had improved OS (HR = 0.33, P <0 .0001) and DFS (hazard ratio [HR] = 0.45, P < 0.0001), at 6.5 years of follow-up, confirming that pCR can be used as a surrogate marker for improved long-term prognosis. The results of NSABP B18 and B27 with an extended follow-up of 16 and 8.5 years' respectively have also been published (21). In both protocols the results demonstrate that preoperative therapy is equivalent to adjuvant therapy and there are no statistically significant differences in OS and DFS. Hence, in NSABP B-18 trial there were trends in favor of pre-operative chemotherapy for disease-free survival (DFS) and OS in women less than 50 years old. In addition, preoperative DOC added to AC significantly increased the proportion of patients having pCRs compared with preoperative AC alone (26% *vs* 13%, P< 0.0001). In both studies, patients who achieved a pCR continue to have significantly superior OS and DFS (21).

Many other studies compared neoadjuvant and adjuvant chemo-endocrine therapies (22,23), including different regimens in pre- and post- operative setting (24-26). In general, comparable results appear with either approach and with no overall substantial differences. A meta-analysis that was published in 2005 by Mauri et al. (27) included nine randomized studies. They compared neoadjuvant *vs* adjuvant therapy, regardless of regimen and local therapy. In accordance with all previous trials, this meta-analysis did not reveal substantial difference between the two treatment settings in disease progression, distant recurrence rates or mortality. On the other hand, NCT was associated with an increased risk of loco-regional recurrence compared to adjuvant therapy. The conclusion was that NCT

and adjuvant chemotherapy had equivalent rates of survival and disease progression.

Dan Costa et al. (28) performed a secondary analysis of the GeparTrio trial Data. NCT shows similar response in patients with OBC and LABC/IBC. In this study although response rates (RR), clinical (c) and pCR presented significant differences in the subgroups, in multivariable analysis tumor stage was not an independent predictor for pCR. At least to our knowledge, none of the other trials in NCT, provides a direct comparison of LABC/IBC with OBC results. Data from this study provide for the first time, direct evidence for similar response patterns throughout all stages of breast cancer. Based on this observation one might attempt to extrapolate results of the OBC trials to LABC populations (28).

Summarizing, these trials have shown that NCT is well tolerated and significantly improves outcomes compared to surgery alone, with at least comparable results to those of adjuvant chemotherapy. The latter has largely contributed to the establishment of NCT as part of standard treatment in patients with LABC.

The critical question: which regimen and for how long?

The choice of the optimal chemotherapy regimen and the duration of treatment have been extensively assessed in induction systemic chemotherapy but no consensus has been developed so far. Beyond the pivotal data from early anthracycline and CMF-like containing studies of NCT, more recent randomized trials in LABC focus on the addition of newer agents. All these trials are based to well established regimens used in the adjuvant setting research.

The study of Hutcheon et al. (29) was one of the early phase III randomized trials in LABC patients that confirmed the superiority of the sequential neoadjuvant approach of 4 cycles of an anthracycline regimen followed by 4 cycles of DOC-based regimen. This regimen was compared to 8 cycles of an anthracycline regimen alone. A high number of relative trials evaluated the role of different combinations of anthracyclines and taxanes. The Aberdeen Breast Study Group has conducted a two arm randomized trial (30,31) that compared eight cycles of neoadjuvant cyclophosphamide, vincristine, doxorubicin and prednisone (CVAP) *vs* four cycles of neoadjuvant CVAP followed by four cycles of neoadjuvant DOC. Significantly greater RRs (85% *vs* 64%), pCR rates (31% *vs* 15%), 5 year OS (93% *vs* 78%) and also incidence of breast-conserving surgery (67% *vs* 48%), were observed for patients in the DOC containing arm. This result suggests that the use of sequential, non-cross-resistant chemotherapeutic agents, such as anthracyclines and taxanes, can improve survival. Instead, pCR was only 2% in the subgroup of patients with initially stable or progressive disease to CVAP that then switched to DOC. This suggests that initial no responders do not benefit from switching to another regimen.

The study of Evans et al. (32), a well designed randomized trial, compared the clinical and pathologic RR of AC *vs* doxorubicin and docetaxel (AT), as primary chemotherapy in women with LABC. In contrast to the positive results reported for the sequential use of DOC after AC as induction chemotherapy, this study did not suggest a benefit for simultaneous AT over AC. However, encouraging were the results of a small non randomized trial in stage III breast cancer patients treated with NCT. Four cycles of DOC single therapy resulted in a 7% pCR rate in the breast and axilla (95% CI 2% to 21%) and a 5-year overall survival rate of 80% (33). Another randomized trial of Untch et al. (34), evaluated the role of a dose-dense sequential schedule of epirubicin (E) and paclitaxel (PAC). A significantly higher frequency of breast conserving surgery and a higher pCR rate were observed as compared to E/PAC in standard dose.

With a similar design in the GEPAR-DUO study (35), the dose-dense combination of A plus DOC administered for four cycles has resulted to a clinical RR of 73% and pCR of 7%. Preliminary results, from a small phase II trial (31), with the use of a neoadjuvant DOC and vinorelbine (V) regimen appear promising, with an RR of 100%, cCR rate of 59% and pCR rate of 31%. Another recent report, evaluates the activity and safety of a non anthracycline-regimen, containing PAC plus carboplatin, in 107 patients with bilateral breast cancer (36). Clinical RR was 86.1% (CR: 32.4%) while twenty-one patients achieved pCR (19.4%).

Many other phase II and III trials have studied the role of taxanes in pre-operative setting. These trials have been highly heterogeneous with different patient populations. They often included operable and inoperable disease and a mixture of node-positive and node-negative patients. Furthermore, regimen selections varying between sequential and combination schedules, with different number of cycles. However, the use of taxanes in the induction therapy setting seems to be associated with improved outcomes in various endpoints assessed (37-44). In these studies sequential administration of an anthracycline and DOC in the neoadjuvant setting resulted in clinical RRs ranging from 85% to 93% and pCR rates from 11% to 31%. For anthracycline and DOC in combination setting, clinical RRs and pCR rates range from 68% to 93% and 8% to 16%, respectively.

Other non taxane-containing regimens and alternative schedules have been tested in NCT. Of special interest is the phase III randomized study of Therasse et al. (45). In this study a preoperative anthracycline-based regimen was compared with a similar regimen with dose intensification. The dose dense arm was not superior. It should be noted that due to discrepancies between the two arms the interpretation of the results is difficult and no safe conclusion could be extracted.

Another promising approach is that of metronomic dose

scheduling in neoadjuvant setting. A phase III study of Ellis et al. (46) (SWOG trial 0012) evaluated this approach. In this study, 265 patients with LABC were randomized to conventional AC *vs* metronomic dosing of A, 24 mg/m^2 weekly, and C, daily oral 60 mg/m^2 plus growth factor-support for 15 weeks and then both arms followed by standard weekly PAC for 12 weeks. Preliminary results of this trial suggest an improved pCR rate (19% *vs* 31%, respectively; OR=2.11, *P*=0.020) with the metronomic schedule. The pCR improvement was most pronounced in the inflammatory cohort (12% *vs* 32%). Many other different regimens have been tested with positive results, although no definitive advantage has been demonstrated for any of them (47-55).

Moreover, the duration of induction chemotherapy remains an unresolved issue and no optimal approach has been established. The maximal response to NCT vary widely; there are patients who achieve maximal tumor reduction after only one or two cycles, while others require up to eight or more cycles of treatment, as evidenced from cumulating clinical experience.

The optimal duration of induction treatment with concurrent taxane and anthracycline containing regimen was also addressed in the phase III randomized GeparTrio trial (56). In this study, 2,090 women with advanced disease were initially treated with two courses of docetaxel, adriamycin, cyclophosphamide (TAC). Responders were then randomly assigned to four versus six additional cycles of TAC, while non responders were assigned to four additional cycles of TAC or to crossover to a non anthrcycline regimen with vinorelbine (V) plus capecitabine (CAP). Among responders, those who received eight courses of TAC had significantly higher c RR, but the pCR rates were comparable: 24% *vs* 21% for eight and six cycles, respectively. These data suggest that more than six cycles of TAC do not improve RR, although OS was not addressed. Few more randomized trials have been undertaken in an attempt to set cut off point (57,58).

Summarizing, until the era of taxanes the common practice was the use of an anthracycline-based regimen for a minimum of three to four cycles. Additional courses of the same regimen administered until reaching a "plateau" of maximal clinical response and frequently continued for two cycles beyond this clinical cut off point. This approach was felt to maximize the rate of complete remission. However, as noted above, emerging data suggest that both responders and non responders to four cycles of an initial anthracycline-based regimen benefit from crossover to a non cross-resistant therapy, usually a taxane and the trend is to administer the most of systemic chemotherapy before the local treatment.

Utility of initial response: an important predictive factor?

One more issue that was subject of extensive debate in NCT is the importance of response to initial chemotherapy. This variable is an established key criterion of the early era of induction chemotherapy trials. It represents the main advantage of preoperative therapy, which is the feasibility to monitor tumor response and to tailor subsequent treatment based on response. Nevertheless, no strong correlation of clinical and pathologic responses has been demonstrated (11).

Although early clinical response is associated with higher rates of pCR and better long-term outcome (59), trials have not verified an outcome improvement when treatment planning is based on clinical response (11). In the GeparTrio (56) and the Aberdeen (60) trials the subgroup of patients with clinically non responding disease presented low pCR rate. That was not consistently improved by switching to a non- cross-resistant chemotherapy regimen. Although both studies used a similar randomization (continue treatment or switch to a new regimen), they were different in the randomization timing (4 *vs* 2 cycles) and disease characteristics (sensitive *vs* resistant disease). Nevertheless, both studies suggested that the treatment plan should not be altered based on early response. Unless there is a clear evidence of disease progression, deviations from the planned therapy in clinical non responders do not increase either pCR or clinical response rate (cRR) nor improve survival (56,60). However, in the early NSABP B-27 trial, subgroup analysis in those patients who had a clinical partial response after AC indicates that there was a significant DFS benefit when adding four cycles of preoperative DOC to AC.

Of different design was the study by Thomas et al. (61), which evaluated the benefit of adding adjuvant chemotherapy when NCT does not induce a pCR. In this trial, 193 patients with LABC received neoadjuvant CAVP and had a c RR of 83.4% and a pCR rate of 12.2%. The patients, who did not achieve pCR, were randomized to receive additional CAVP or vinblastine, methotrexate, leucovorin, and fluorouracil (VbMF). Disease-free and OS rates were not statistically different between the two groups, suggesting little benefit to postoperative chemotherapy when NCT does not induce a pCR.

In summary, pCR to NCT has been consistently associated with improved DFS and OS and early clinical response usually correlates with high probability for pCR. On the other hand, even data extracted from several trials that evaluated early clinical response as an important parameter, we should be cautious when it is used as a criterion for early or mid-treatment modulations. Some of the most important early trials are summarized in Table 1 (62-80) and furthermore, selected ongoing phase III randomized trials in NCT are presented in Table 2.

Neoadjuvant targeted therapy regimen

The main pathways undergoing therapeutic targeting are currently HER-2 and angiogenesis. For HER-2 targeting therapies already exist enough data reported from phase III trials.

Table 1. Selected early trials in Neoadjuvant chemotherapy in Breast cancer (LABC/IBC and OBC)

Study	No. of patients	Stage	Overall RR	pCR	DFS	OS
de Lena et al.(62), 1978	110	T3b-T4	70%	n/a	n/a	52.8%(at 36mo)
Hortobagyi et al.(63), 1983	52	IIB-IIIC	82%	n/a	40%(at 60mo)	53%(at 60mo)
Ragaz et al.(64), 1985	43	IB-IIIB		n/a	86%(at 24mo)	96.7%(at 24mo)
Swain et al.(65), 1987	76	IIIA-IV	93%	36% (in cCR pts)	59%(at 26.4mo)	76%(at 26.4mo)
Jacquillat et al.(66), 1988	98	IIIA-IIIB	91%	n/a	62%(at 36mo)	77%(at 36mo)
Hortobagyi et al.(67), 1988	174	III	NR	n/a	84%(IIIA),33%(IIIB) (at 60mo)	84%(IIIA),44%(IIIB) (at 60mo)
Perloff et al.(68), 1988	113	III	72%	n/a	n/a	n/a
Valagussa et al.(69), 1990	277	III	62%	34%	n/a	n/a
Pierce al.(70), 1992	107	IIB-IIIC	57%	29%	n/a	61%(IIIA),28%(IIIB), 36%(T4d) (at 60mo)
Schwartz et al.(71), 1994	189	IIB-IIIB	85%	17%	61%(at 60mo)	69%(60mo)
Smith et al.(72), 1995	50	IIB-IIIB	98%	27%	n/a	n/a
Ueno et al.(73), 1997	172	T4d	74%	n/a	32%(at 60mo)	40%(at 60mo)
Touboul et al.(74), 1997	147	IIA-IIIA	59%	n/a	n/a	65%(at 120 mo)
Brain et al.(75), 1997	107	II-III	70%	n/a	25%(III), 51%(IIB), 82%(IIA) (at 81mo)	n/a
Bonadonna et al.(76), 1998	536	II-III	76%	n/a	31-37% (at 96mo) (according to T stage)	n/a
Kuerer et al.(77), 1999	372	III	n/a	12%	n/a	n/a
Ezzat et al.(78), 2000	72	IIB-IIIB	90%	22%	81%(22mo)	93%(22mo)
Cristofanilli et al.(79), 2001	42	T4d	81%	14%	n/a	n/a
VanPraagh et al.(80), 2001	29	IIA-IIIB	87.5%	11,1%	n/a	n/a

RR: response rate; pCR: pathologic complete response; DFS: disease free survival; OS: overall survival; mo: months; n/a: not available.

Table 2. Selected ongoing phase III randomized trials in Neoadjuvant Chemotherapy

Trial	Target accrual (No. of patients)	Therapy Arms
GeparQuatro	1150	Epirubicin(E)-Cyclophosphamide(C) X4 followed: a.Docetaxel (DOC)X4 b.DOC-Capecitabine (CAP) c.DOC X4 → CAP-Trastuzumab (TRAST)
GeparQuinto	600	In HER2(+ve) patients: a.EC X4 → DOC X4+ TRAST b.EC X4 → DOC X4+ Lapatinib (LAP) In HER2(-ve) patients: a.EC X4 ± Bevacizumab (BEV) → 1.responders: DOC X4 + BEV 2.non responders: a.Paclitaxel (PAC)(weekly)+Everolimus b.PAC (weekly)
NSABP B-40	1200	In HER2 (-ve) patients: *six arm* design comparing complex combinations of: DOC, Doxorubicin (A)-C, BEV, CAP, Gemcitabine
NSABP B-41	520	In HER2(+ve) patients: *three arm* design comparing combinations of: sequential AC with PAC followed by, TRAST, LAP or TRAST +LAP
NEOALTO	450	In HER2(+ve) patients: *three arm* design comparing combinations of: a.TRAST → PAC → TRAST b.LAP → PAC → LAP c.TRAST+ LAP → PAC → TRAST + LAP All followed by 5-FU(F), E, C x3
ACOSOG Z1041	270	In HER2 (+ve) patients: *two arm* design comparing combinations of: a.FEC → PAC+ TRAST b.PAC+TRAST → FEC+ TRAST

→ : sequential use of agents; + : concominant use of agents.

On the contrary, data on anti-angiogenetic agents are limited so far.

a. HER-2 targeting therapy

Trastuzumab (TRAST) is a humanized monoclonal anti-HER2 antibody approved for the treatment of HER2-positive (+ve) breast cancer either in the adjuvant or metastatic setting. It is used either as a single agent after chemotherapy or in combination with chemotherapy. Several trials have examined the potential benefits of neoadjuvant TRAST combined with chemotherapeutic agents in patients with HER2+ve tumors (81-83). In this review, we are going to focus only to phase III trials presented so far.

Buzdar and colleagues (84) conducted a phase III trial to assess NCT consisting of PAC, 5-FU, E and C with or without TRAST. The pCR rate was 65.2% in the TRAST arm *vs* 26.3% in the chemotherapy-only arm (P=0.016). The 3-year DFS rate (100% *vs* 85.3%, respectively) improved with TRAST addition. Furthermore, in the NOAH (neoadjuvant Herceptin) trial (85), patients with HER2+ve locally advanced or inflammatory breast cancer were randomized to CT (A, PAC, CMF-regimens) with or without TRAST. In addition, a subgroup of patients with HER2-negative(-ve) disease treated with the same chemotherapy combination was used as control. TRAST significantly improved event-free survival in patients with HER2+ve breast cancer in 3 years [71% (95% CI: 61-78) with TRAST *vs* 56% (95%

CI:46-65) without]. Overall response rate was 87% in the TRAST arm *vs* 74% without TRAST (*P*=0.009). Response rates did not differ in patients with HER2+ve disease who were not treated with TRAST compared to those with HER2-ve disease.

In the GeparQuattro study (86), four cycles of EC followed by four cycles of DOC with or without CAP and TRAST were administrated to patients with operable or locally advanced HER2+ve tumors. Furthermore, a subgroup of patients with HER2-ve disease was treated with the same chemotherapy regimen. In HER-2+ve disease patients, pCR was 31.7% *vs* 15.7% in HER2-ve group of patients. Despite the high pCR rate, TRAST in patients with HER2+ve disease did not result in a higher rate of breast-conserving surgery.

TRAST in previously described studies was well tolerated and chronic heart failure rates reported were <1%. Patients who are candidates for NCT have a high probability to achieve a pCR if they have HER2+ve tumors. Application of TRAST should be considered to improve clinical and pathological tumor RR and outcome.

Lapatinib (LAP), an oral agent that inhibits HER1 and HER2 receptor tyrosine kinase, is already approved for use in HER2+ve metastatic breast cancer after progression on anthracyclines, taxanes, and TRAST. A phase II trial of LAP in refractory/relapsed IBC reported a c RR of 50% on skin lesions and a 28% overall RR (87). Cristofanilli et al. (88) studied LAP monotherapy followed by LAP and weekly PAC in patients with newly diagnosed IBC. A c RR of 77% and a pCR of 17% in patients with HER2+ve IBC were reported.

b. Anti - angiogenesis treatment

Bevacizumab (BEV) is a recombinant, humanized, monoclonal anti- VEGF antibody that targets angiogenesis, vascular permeability, and endothelial cell growth. Its synergy and efficacy with other chemotherapeutic agents in metastatic breast cancer was studied in preclinical and phase I, phase II studies but also confirmed in phase III trials (89-94). Data with BEV in the neoadjuvant setting are limited to date.

In 2004, a phase II trial of neoadjuvant DOC with or without BEV in LABC was presented. Five CR and 24 PR were observed (95). Wedam et al. (96) reported on 21 patients with LABC treated with BEV on cycle 1 and ADOC and BEV for 6 more cycles. A c RR of 67% (95% CI: 43% - 85.4%) with a 5% pCR rate was observed. In addition, a median decrease of 66.7% in phosphorylated VEGFR2 in tumor cells (*P*=0.004) and increase of 128.9% in tumor apoptosis (*P* =0.0008) were seen after BEV alone. Furthermore, these results persisted with the addition of chemotherapy.

Hurvitz et al. (97) reported on a multicenter phase II trial of neoadjuvant single-agent BEV or placebo, followed by TAC, with or without BEV, in patients with stage II or stage III breast cancer [Arm A: TAC + low-dose BEV (7.5 mg/kg); Arm B: TAC + low-dose placebo; Arm C: TAC + standard dose BEV (15 mg/kg); Arm D: TAC + standard-dose placebo]. 90 patients were initially enrolled. Of the 37 post- surgery patients, clinical CR rate was 59% (5/12 Arm A; 7/11 Plac- Arms B/D; 10/14 Arm C) and 35% clinical PR (7/12 Arm A; 3/11 Arms B/D; 3/14 Arm C).

In a phase II pilot study (98) in HER2-ve patients DOC, CAP and BEV combination was evaluated. pCR rate was 22% (95% CI: 6-48). Nine of the patients without pCR achieved clinical partial response, giving a 72% overall clinical RR (95% CI: 47-90). Waintraub and colleagues (95) presented their results of neoadjuvant dose-dense BEV plus DOC followed by a BEV-AC regimen in HER2-ve LABC. Fifteen patients were enrolled and of the first 12 post-operative evaluable patients the results showed 5 pCR (42% pCR rate). In a multicenter pilot study Yardley et al. (100) presented results of weekly nab-paclitaxel, carboplatin, BEV and TRAST as neoadjuvant therapy in HER2-ve LABC; pCR was noted in 13/20 patients (65%) and PR was noted in 7/20 patients (35%).

It is obvious that available data are scarce so far and large prospective phase III trials are warranted to evaluate BEV's and other antiangiogenic agents', as sunitinib and sorafenib, efficacy in the neoadjuvant setting. Preliminary safety data are recently reported by GeparQuinto study on BEV or everolimus or LAP addition to anthracycline- and taxane-based neo-adjuvant chemotherapy regimens in primary breast cancer. Adding BEV and everolimus to chemotherapy appeared feasible, meanwhile it is suggested a decrease of LAP dose to 1000 mg daily (101).

c. Preliminary data of attractive agents

Preclinical and preliminary clinical data indicate that Zolendronic acid through farnesyl diphosphate synthase inhibition has both direct and indirect antitumour effects in breast cancer (102). In the adjuvant setting, its addition to endocrine treatments seems to improves outcomes in pre-menopausal women with early breast cancer (99). Performing a retrospective evaluation within AZURE (Adjuvant Zoledronic acid redUce REcurrence) trial the clinical data extracted suggested that the addition of Zolendronic acid to neoadjuvant CT may improve pathological response (104).

In vitro and *in vivo* data support a role of insulin in carcinogenesis. Metformin, an oral antidiabetic agent that increases insulin sensitivity and reduces insulin levels was studied in a retrospective analysis in combination with neo-adjuvant chemotherapy. A pCR rate of 24% in the combination arm compared to 8% in patients who were not receiving metformin was observed (*P* =0.02) (105).

Conclusion

Neoadjuvant chemotherapy integrated into a multimodality

program is the established treatment in LABC. Although efforts in this field of research are ongoing, the integration of anti-HER2 and other biological therapies, as anti-angiogenesis targeting treatments, has major clinical importance, since it has the potential to further improve the long term control of LABC. Identifying which tumors are most likely to respond to specific agents and regimens could significantly improve prognosis. Clinical management of LABC could be modified based on advances in our knowledge of cancer biology and genomic profiling to a highly effective individualized approach.

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