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CLINICAL TRIAL

Pathological complete response rates following different neoadjuvant chemotherapy regimens for operable breast cancer according to ER status, in two parallel, randomized phase II trials with an adaptive study design (ECTO II)

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Abstract Sequential doxorubicin/paclitaxel (AT) followed by CMF treatment was shown to be an active neoadjuvant chemotherapy regimen in the first European Cooperative Trial in Operable Breast Cancer (ECTO I trial). The aim of the current study (ECTO II) is to assess the complete pathological response (pCR) rate following three different anthracycline and taxane-containing neoadjuvant chemotherapy regimens, with or without capecitabine (X). Patients with operable, invasive breast cancer >2.0 cm in diameter, were randomized to AT→CMF, AT→CMX or AC→TX regimens in two parallel, randomized, open-label, phase II trials (within a single study) in patients with estrogen receptor negative (ER−) and estrogen receptor positive (ER+) diseases, respectively. Exemestane was delivered concomitantly with neoadjuvant chemotherapy in ER+ tumors. Achievement of pCR was more common in ER− than ER+ women (45.3 vs. 10.4%). Capecitabine was only associated with a higher frequency of pCR in ER+ patients receiving AT→CMX. Overall response rates (ORR) ranged

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from 88 to 97%, and this translated into high rates of breast-conserving surgery (67% of ER− patients and 72% of ER+ patients). All three regimens were well tolerated. Febrile neutropenia and gastrointestinal effects were the most common grade ≥3 adverse events. As expected, the ECTO II study showed higher pCR rates in patients with ER− disease. Substituting capecitabine for fluorouracil (± methotrexate) in anthracycline/taxane-containing regimens appeared to be beneficial only in ER+ tumors. Translational studies investigating interactions between therapeutic agents and tumor biology are warranted to refine patient selection and improve the results of neoadjuvant chemotherapy.

Keywords Chemotherapy · Taxane · Capecitabine · Pathological complete remission · pCR

Introduction

The benefit of primary systemic (neoadjuvant) chemotherapy (PSC) in the treatment of breast cancer, and the association of a pathologic complete response (pCR) with improved disease-free survival (DFS), and overall survival have been shown in a number of studies [1–4]. In particular, the addition of taxanes and the use of sequential non-cross-resistant treatment regimens have resulted in higher rates of pCR [5–7]. Depending on the setting, pCR rates have ranged from 14.3% to 26.1% with such regimens. Accordingly, international expert panels recommend PSC for operable breast cancer when breast-conserving surgery (BCS) is not possible, and tumor markers at diagnosis suggest good response to chemotherapy [8, 9].

Analyses after longer follow-up have revealed that achievement of a pCR can translate into survival benefit [10]. Women who achieved a pCR in the NSABP B-27 trial had a significantly higher survival rate compared to those without a pCR (hazard ratio [HR] 0.33; $P < 0.0001$) after a median follow-up of 6.5 years. In the first European Cooperative Trial in Operable breast cancer (ECTO I), in which the efficacy of 4 cycles of doxorubicin and paclitaxel (AT), followed by 4 cycles of cyclophosphamide, methotrexate, and fluorouracil (CMF) was evaluated, distant relapse-free survival was negatively affected by failure to achieve a pCR (HR 0.43; $P = 0.025$) [11].

Currently, negative hormone receptor status is the strongest predictor of response to chemotherapy [9]. Results of the ECTO I trial showed that pCR was more often achieved in patients with estrogen receptor negative (ER−) than estrogen receptor positive (ER+) tumors (42 vs. 11%; $P < 0.001$) [7]. A regression analysis confirmed that ER status was the only independent variable predicting pCR to chemotherapy ($P < 0.0001$).

The addition of capecitabine to docetaxel or paclitaxel has emerged as a treatment option for patients with metastatic breast cancer pretreated with anthracyclines [12–14], and a pilot study at the Istituto Nazionale Tumori in Milano suggested that capecitabine was an active alternative to fluorouracil for use in combination with cyclophosphamide and methotrexate (CMX) [15]. New therapies are also available with the potential to improve on results of the sequential AT→CMF regimen. However, definitive Phase III studies require thousands of patients. The ability of primary tumor eradication to predict efficacy outcome [2, 16] provides a means for selecting the most promising PSC regimens for further study, using smaller patient populations.

The aim of this study (ECTO II) was to assess the pCR rate following three different anthracycline and taxane-containing neoadjuvant treatment regimens (including the previously evaluated AT→CMF regimen), in patients with ER− and ER+ operable breast cancer. ER− and ER+ patients were enrolled in two parallel, randomized, open-label phase II trials, within the same (ECTO II) study.

Patients and methods

Study design

This was a multicenter, open-label study (EudraCT 2004-004957-24, ISRCTN 96423607), comprising two parallel, randomized, 3-arm Phase II trials; one trial enrolling ER− and the other trial enrolling ER+ patients (Fig. 1). The study was performed at 23 centers in 4 countries. Randomization was performed by the Michelangelo

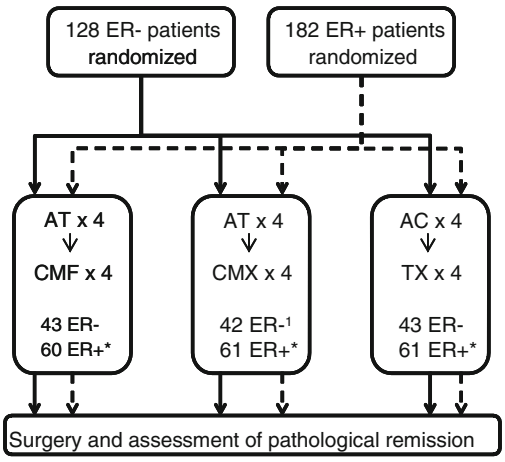

Fig. 1 Design and patient disposition in the two parallel, phase II trials constituting the ECTO II study. 128 women with ER− and 182 women with ER+ operable breast cancer were enrolled. One patient assigned to AT→CMX in the ER− trial withdrew consent before starting therapy. This patient remained in the intent-to-treat (ITT) population but was not considered for the safety analysis. (*A* doxorubicin; *C* cyclophosphamide; *F* fluorouracil; *M* methotrexate, *T* paclitaxel; *X* capecitabine)

Operations Office in a ratio of 1:1:1 with stratification for geographical area, primary tumor diameter ($\leq$4.0 vs. >4.0 cm), human epidermal growth factor receptor-2 (HER2), and progesterone receptor (PgR) status. The primary objective was the assessment of pCR rates in response to three different chemotherapy regimens in ER− and ER+ patients. Secondary objectives were overall clinical response rate (ORR) after the first treatment sequence (4 cycles) at the end of PSC, and the tolerability, and safety of the investigated regimens. The study protocol, accompanying materials and amendments were approved by the local Independent Ethics Committees. All patients had to provide written informed consent before any study-specific screening procedure.

Patients

Eligible patients had to be females $\geq$18 years old, presenting for the first time with unilateral, operable, invasive breast cancer >2.0 cm in diameter, with no previous treatment for invasive malignancy, and an Eastern Cooperative Oncology Group (ECOG) performance status $\leq$1. Sufficient tissue for receptor status and translational studies was mandatory. Exclusion criteria included bilateral, metastatic or locally advanced breast cancer, prior or concomitant invasive malignancy, prior hormone-, chemo- or radiotherapy for any malignancy, New York Heart Association (NYHA) class $\geq$II heart disease, left ventricular ejection fraction (LVEF) <50% or a history of congestive cardiac failure or angina pectoris, a history of uncontrolled central nervous system disorders, grade >1 motor or sensory neuropathy, abnormal baseline hematologic values, pregnancy or lactation. Patients of child-bearing potential had to use adequate contraception.

Hormone receptor status was assessed by immunohistochemistry (IHC) of core biopsy specimens, according to local cut-off levels for positivity. HER2 status was assessed using the Dako Test, at individual centers. Axillary nodal status was assessed before chemotherapy by clinical examination and the primary tumor was marked by skin tattoo.

Treatment

Chemotherapy regimens were identical in the two parallel trials. In arm A, four cycles of AT (doxorubicin 60 mg/m^2 i.v. bolus, followed by paclitaxel 200 mg/m^2 infused over 3 h) were given at 3-week intervals, followed by four cycles of CMF (600 mg/m^2 cyclophosphamide, 40 mg/m^2 methotrexate, and 600 mg/m^2 fluorouracil i.v. on days 1 and 8) at 4-week intervals. In arm B, four AT cycles as described for arm A were followed by four cycles of CMX (600 mg/m^2 cyclophosphamide and 40 mg/m^2 methotrexate i.v. on days 1 and 8, and 1850 mg/m^2 oral capecitabine divided into two daily doses from day 1 to 14) at 4-week intervals. Arm C comprised four cycles of AC (60 mg/m^2 doxorubicin, 600 mg/m^2 cyclophosphamide) at 3-week intervals followed by four cycles of TX (100 mg/m^2 paclitaxel i.v. over 1 h on days 1 and 8, and 1850 mg/m^2 oral capecitabine in divided doses from day 1 to 14) at 3-week intervals.

Patients with ER+ disease (trial 2) also received 25 mg/day of oral exemestane from the first day of doxorubicin until the day of surgery, plus luteinizing hormone releasing hormone (LH-RH) analogs in premenopausal patients. At the time the study was conducted, trastuzumab was not established for PSC and accordingly, pre-operative trastuzumab was not permitted.

All patients were clinically evaluated for response after every cycle and underwent mammography $\pm$ echography after each treatment sequence. Patients with tumor progression during therapy proceeded directly to surgery.

Surgery was performed 3–4 weeks after the last dose of PSC, according to the judgment of the local surgeon, taking into account patient preference, tumor size, focality, and cosmetic aspects. Axillary lymph node dissection was required up to the second level at least (or sentinel node dissection). All patients who had BCS received postoperative irradiation. It was recommended that radiotherapy should start 4–6 weeks after surgery and that the breast should be irradiated with two opposing tangential fields. Treatment should consist of 5 fractions a week to a total dose of 50 Gy. A boost of 10 Gy in 5 fractions could be given to the tumor bed. After mastectomy, irradiation of the chest wall with electrons was mandatory for pT4 cases, with a total suggested dose of around 45 Gy.

Pathologic evaluation at surgery

The extent and type of residual tumor in the post-treatment surgical specimens were evaluated microscopically by local pathologists according to predefined pathological guidelines for the study. In brief, these required sectioning at intervals of 5 mm to 1 cm, and evaluation of all grossly and radiographically suspicious areas**,** in addition to the tumor 'bed' (the former tumor area) in patients achieving a pCR. For patients undergoing breast conservation, the entire specimen was to be evaluated. Surgical margins had to be checked for the presence of invasive or in situ disease. The number of positive and negative nodes was to be assessed (three sections of each lymph node was suggested). Reassessment of ER, PgR, and HER2 status was advised, using the same procedures as at the pre-treatment evaluation.

Postoperative systemic treatment and follow-up

Decisions on postoperative systemic therapy were made by local investigators but reported to the Michelangelo Operations Office. It was recommended that all patients be followed for at least 5 years, and that endocrine therapy (for patients with ER+ tumors) and adjuvant trastuzumab (for patients with HER2 positive [HER2+] tumors) be given according to international guidelines.

Safety assessment

Side effects were assessed at every treatment cycle and graded according to the Common Toxicity Criteria for Adverse Events (CTCAE) Version 3.0. Cardiac function was evaluated (by electrocardiogram and LVEF) after each treatment sequence and graded according to the NYHA classification. During the 5 year follow-up period, physical examination, blood chemistry, and a complete blood count were recommended every 6 months, and assessments of cardiac function once a year.

Statistical methods

The primary endpoint of the two trials within the study was pCR rate, defined as pCR in breast. The objective of the study was to identify the most promising of the three possible regimens in patients with ER− and ER+ breast cancer. The trials were designed to have a 90% probability of identifying a treatment regimen with at least a 15% increase in activity compared with the activity of the AT→CMF regimen, using a so-called 'pick the winner' design [17, 18]. Based on previous results [7], pCR rates <50% in ER− and <10% in ER+ tumors were considered clinically uninteresting, and pCR rates of ≥65% and ≥25%, respectively, were considered clinically worthwhile. To allow for the early termination of ineffective treatment arms, a two-stage design was used. In the first stage, 42 ER− and 28 ER+ evaluable patients would be enrolled in each arm of the respective trials. If there were fewer than 23 pCRs in an ER− trial arm or fewer than 4 pCRs in an ER+ trial arm, accrual to the respective arm would be terminated. In the second stage, randomization would continue to the promising treatment arms until 105 (ER−) or 57 (ER+) patients were enrolled in each arm. If one arm achieved ≥60 pCRs (ER−) or ≥10 pCRs (ER+) compared with <30 pCRs (ER−) or <5 pCRs (ER+), the schedule with the most pCRs would be declared the winner. If two arms in one of the trials achieved the desired level of activity, selection of the preferred regimen would depend on other factors, such as toxicity, feasibility, and/or convenience.

The primary and secondary efficacy variables were analyzed for the full analysis set (intent-to-treat principle, as randomized). The safety population comprised all randomized patients who received at least one dose of study medication.

Results

Patient characteristics

A total of 128 ER− (first stage only) and 182 ER+ patients (including 86 ER+ patients in the first stage) were randomized to the three treatment arms in the two parallel trials (Fig. 1). Clinical and disease characteristics were well balanced between the arms and comparable between the two trials (Table 1). However, as expected, patients with ER+ disease were less likely to have high grade, HER2+ (IHC = 3), or PgR− tumors than patients with ER− disease.

Treatment response and surgery

In patients with ER− tumors, pCR rates were 53.5% for the AT→CMF regimen, 40.5% for AT→CMX, and 39.5% for AC→TX (Table 2). Complete absence of invasive disease in both breast and nodes (tnpCR) was documented in 44.2, 35.7, and 37.2% of patients, respectively. Since the early stopping hurdle of 23 pCRs was only passed in the AT→CMF arm, the ER− trial was closed after the first stage. The overall clinical response rates in the three arms were 95, 88, and 93%, respectively (Table 3). Only two women experienced tumor progression (one during AC and one during CMX treatment). BCS was feasible in 67% of patients with similar rate across the three arms. The rate of BCS was 81% in ER− patients who achieved a clinical CR and 54% in those who achieved a partial response (PR).

In patients with ER+ tumors, pCR rates were 5.0% for the AT→CMF regimen, 16.4% for AT→CMX, and 9.8% for AC→TX (all with additional exemestane ± LHRH; Table 2). Rates of tnpCR were 3.3, 13.1, and 8.2%, respectively. After the first stage (86 patients enrolled), the efficacy criterion of 4 pCRs was met in all three arms and so recruitment continued to a total of 182 patients. One pCR diagnosed in the AT→CMF arm at interim analysis was not confirmed at final analysis. The ORR in the three arms was 97, 93, and 97%, respectively (Table 3). Overall, 72% of ER+ patients were eligible for BCS after the primary systemic therapy: 81% of patients who achieved a clinical CR, and 67% of those who achieved a PR.

Tolerability and safety

The percentage of patients receiving >85% of planned doses of chemotherapy was similar in both trials, ranging from 89 to 95% for the initial AT and AC cycles, and from

Table 1 Baseline patient characteristics

	ER− patients			ER+ patients		
	AT→CMF	AT→CMX	AC→TX	AT→CMF	AT→CMX	AC→TX
Patients (#)	43	42	43	60	61	61
Age (median, years)	47 (29–71)	53 (34–77)	47 (24–70)	50 (30–67)	49 (28–73)	48 (27–67)
cT 2–4 cm (%)	70	69	67	70	70	70
cT > 4 cm (%)	30	31	33	30	30	30
cN0 (%)	44	45	49	40	43	41
cN1–2 (%)	56	55	49	60	57	59
cN3 (%)	–	–	2	–	–	–
G3 (%)	63	52	37	23	23	23
PgR− (%)	93	93	91	18	18	16
HER2 3+ (IHC, %)	35	36	33	18	18	18
LVEF (median, %)	62 (51–76)	68 (50–76)	64 (50–75)	68 (51–80)	67 (56–80)	65 (50–77)

cT clinical T, *cN* clinical N, *A* doxorubicin, *C* cyclophosphamide, *F* fluorouracil, *M* methotrexate, *T* paclitaxel, *X* capecitabine

Table 2 Pathological remission (non invasive, intent-to-treat)

	ER− patients			ER+ patients		
	AT→CMF	AT→CMX	AC→TX	AT→CMF	AT→CMX	AC→TX
Patients	43	42	43	60	61	61
pCR (95% CI)	53.5% (37.7–68.8)	40.5% (25.6–56.7)	39.5% (25.0–55.6)	5% (1.0–13.9)	16.4% (8.2–28.1)	9.8% (3.7–20.2)
tnpCR (95% CI)	44.2% (29.1–60.1)	35.7% (21.6–52.0)	37.2% (23.0–53.3)	3.3% (0.4–11.5)	13.1% (5.8–24.2)	8.2% (2.7–18.1)
pN0 (95% CI)	72.1% (56.3–84.7)	66.7% (50.5–80.4)	65.1% (49.1–79.0)	48.3% (35.2–61.6)	55.7% (42.4–68.4)	52.5% (39.3–65.4)

pCR in breast pathological complete response (primary endpoint); *tnpCR* complete response in breast and nodes; *pN0* pathologically node-negative

Table 3 Clinical response rate (intent-to-treat)

	ER− patients			ER+ patients		
	AT→CMF	AT→CMX	AC→TX	AT→CMF	AT→CMX	AC→TX
Patients	43	42	43	60	61	61
CR (#)	18→28	12→17	12→24	10→26	12→26	8→25
PR (#)	17→13	22→20	21→16	37→32	37→31	42→34
NR (#)	4→1	3→1	5→0	9→1	9→1	9→1
PD (#)	0→0	0→1	1→1	0→0	0→0	0→0
NA (#)	4→1	5→3	4→2	4→1	3→3	2→1
Total CR (%)	65	40	56	43	43	41
Total ORR (%)	95	88	93	97	93	97

CR complete remission; *PR* >50% partial remission; *NR* no or minor remission; *PD* progressive disease; *NA* not available; *ORR* overall response rate

73 to 94% for the subsequent (CMF, CMX or TX) cycles. Fewer patients (~80%) received >85% of planned doses of capecitabine-containing treatment (CMX or TX) compared with CMF (≥90%).

Leukopenia and neutropenia were the commonest hematologic toxicities, with higher rates reported in the later (CMX, CMF or TX) cycles of therapy (Table 4). Two percent of ER− patients (no ER+ patients) experienced grade 3 thrombocytopenia. Febrile neutropenia and gastrointestinal effects were the most common grade ≥3 adverse events. Gastrointestinal side effects (nausea and vomiting) were the only grade ≥3 adverse events that were observed in >10% of patients (CMX sequence in ER+ patients). Cardiac events were only reported in ER+ patients (4% of patients during AC and 2% during TX). Overall, only one transient decrease in LVEF (ER+ patient) and no hand and foot syndrome of grade ≥3 were reported. There was one toxic death: a patient receiving CMF chemotherapy died of *Pneumocystis carinii*.

Table 4 Main NCI-CTC Grade 3 or greater adverse events

	ER− patients					ER+ patients				
	AT	AC	CMF	CMX	TX	AT	AC	CMF	CMX	TX
Patients (#)	84	43	43	41	43	121	61	60	61	61
% of patients										
Treatment delay or adjustment	31	34	52	67	61	17	26	32	51	44
G3 leukopenia	1	0	5	8	2	0	0	2	4	2
G3-4 neutropenia	1	7	5	14	10	4	8	11	11	10
G3 thrombocytopenia	0	2	0	0	0	0	0	0	0	0
G3 anemia	0	0	0	0	2	0	0	0	0	0
Pancytopenia	1	0	0	0	0	0	0	0	0	0
Cardiac	0	0	0	0	0	0	4[a]	0	0	2[b]
Infection	0	2	5[c]	0	5	2	0	0	0	4
Febrile neutropenia	10	9	9	5	2	9	2	0	4	0
PE/PVT	2	0	0	0	0	3	0	0	4	0
Gastrointestinal	7	10	0	9	9	3	2	2	13	4
Neurosensory	0	0	0	0	5	2	0	0	2	6

[a] atrial fibrillation 2%, hypotension 2%; [b] acute coronary syndrome 2%, [c] one patient with *Pneumocystis carinii*, patient not tested for HIV at study entry. Patient died from multiorgan failure, *PE/TVP* pulmonary embolus/peripheral venous thrombosis

Discussion

Results of the two parallel ECTO II trials of different PSC regimens in women with ER− or ER+ operable breast cancer, confirm the results of previous studies showing a higher pCR and ORR following a range of different chemotherapy regimens in patients with ER− disease versus ER+ disease. In line with previous studies [1], the three sequential non-cross-resistant chemotherapy regimens investigated in ECTO II (AT→CMF, AT→CMX, AC→TX) showed approximately 2.5–10 fold higher pCR rates in patients with ER− compared with ER+ tumors. The same trend was seen for tnpCR rates, although as expected, total eradication of invasive disease in breast and lymph nodes was less frequent than pCR in breast alone, in all patient groups. pCR rates in the AT→CMF arms were comparable to those in the ECTO I trial [7], confirming the interaction between this PSC regimen and ER status seen in the ECTO I trial. However, despite the higher pCR and ORR rates seen in patients with ER− disease compared with ER+ disease, patients with ER− disease were no more likely to undergo BCS in the ECTO II study than patients with ER+ disease. Overall, the majority of patients in both groups were able to have BCS.

In contrast to patients with ER− disease, those with ER+ tumors seemed to benefit from the inclusion of capecitabine in the treatment regimen. Only the AT→CMX regimen in patients with ER+ disease, met the efficacy criterion of ≥10 pCRs, sufficient to be declared the 'winner' according to the trial design. However, it is not possible to conclude that the difference between the AT→CMX arm and the other two arms was significant due to the limited number of patients enrolled, and because no formal comparisons between the treatment arms were planned. The fact that the improvement in activity observed by substitution of capecitabine for fluorouracil was limited to ER+ positive patients while the same substitution had no effect in ER− tumors are in line with recent reports from GerparQuattro and GeparTrio studies showing no benefit from adding capecitabine to neoadjuvant taxane-containing chemotherapies in patients with unselected tumor type [19, 20].

The ORR (93–97%) in ER+ patients treated with combinations of neoadjuvant chemotherapy and exemestane was higher than that reported for neoadjuvant hormonal therapy alone (ORR 39–57%) [21–25]. However, it is not possible to say whether the concurrent administration of exemestane with chemotherapy was beneficial (or detrimental) in this trial. Tamoxifen given concomitantly with adjuvant chemotherapy is known to be inferior to sequential administration, possibly due to a negative interaction of cytostatic tamoxifen and cytotoxic chemotherapy [26]. However, this has not been shown for aromatase inhibitors.

Overall, all three treatment regimens were well tolerated and most patients received >85% of the planned dose. However, treatment delays or modifications were more frequent when capecitabine was part of the combination (Table 4). Febrile neutropenia and gastrointestinal effects were the most common grade ≥3 adverse events. These occurred in 4% and 12% respectively, of patients treated with the CMX regimen, and in 1 and 6% treated with the TX regimen. In comparison, the incidence of grade ≥3 febrile neutropenia and gastrointestinal toxicity was 4 and 1%, respectively, with CMF

treatment. No grade ≥3 hand foot syndrome was documented despite the administration of four cycles of capecitabine in combination with paclitaxel to a proportion of patients. Interestingly, the GeparQuattro trial showed that grade 3/4 hand foot syndrome was more frequent with concomitant capecitabine plus docetaxel (21.4% of patients) than with sequential docetaxel followed by capecitabine (5.6%) [27]. The relatively small differences in grade ≥3 toxicities may cumulatively account for the greater frequency of treatment delays and dose modifications with capecitabine-containing therapy in this trial. Such dose adjustments may be more problematic when longer courses of capecitabine-based therapy (more than 4 cycles) are planned.

Despite the administration of doxorubicin to all patients, only one patient experienced a decline in LVEF, perhaps because the cumulative dose was low (240 mg/m^2).

Despite the higher overall pCR rates in patients with ER− tumors seen in this study, compared to patients with ER+ tumors, patients with ER− disease are known to have a higher relapse rate and worse survival outcome than patients with ER+ disease [9, 28–30]. Furthermore, although patients were treated with effective, non-cross-resistant regimens of anthracyclines and taxanes, fewer than half the patients with ER− tumors in this study achieved a pCR. Thus, there is still a major unmet medical need for new and better therapies, and for translational studies to understand the mechanisms underlying the differences in drug efficacies, and to explore possible interactions between therapeutic agents and tumor biology. The availability of tumor tissue from all patients enrolled in the ECTO II study represents an important opportunity for such context-specific analyses. Importantly, more than 30% of patients with ER− tumors and 18% of patients with ER+ tumors had HER2+ disease but trastuzumab was not given during the neoadjuvant part of the study. Several randomized studies [27, 31–33], and many more non-randomized studies have now shown that the addition of trastuzumab to neoadjuvant chemotherapy significantly improves the pCR rate in patients with HER2+ disease, and long term outcomes for patients treated with neoadjuvant trastuzumab-chemotherapy combinations compared to patients treated with chemotherapy alone [31, 34]. Several new agents (e.g., lapatinib, pertuzumab, neratinib, everolimus) are now being tested in the neoadjuvant setting in patients with HER2+ disease.

Outside the neoadjuvant application, recent data showed that addition of capecitabine into taxane-containing regimens resulted in significant improvement of efficacy in women with early breast cancer [35]. Also in that study the hazard ratio for recurrence free survival tended to be better for ER+ tumors (0.6; CI 0.37–0.96) than for ER− tumors (0.77; CI 0.46–1.27).

Weaknesses of this study include the fact that treatment allocation was not concealed so that bias could potentially have influenced investigator or patient perception of safety or efficacy in the different treatment arms. However, it is unlikely that pathologists would have been aware of or influenced by, treatment regimen in their assessment of surgical specimens. Lack of a central pathologist or pathology panel to review all surgical specimens is another potential weakness since there may be heterogeneity in pathology practice. Use of non-standard neoadjuvant (and adjuvant) endocrine therapy in premenopausal patients could also be criticized. At the time the study was designed, aromatase inhibitors had been shown to be superior to tamoxifen in postmenopausal patients in the adjuvant setting [36, 37]. It was hoped that with concurrent LH-RH agonist therapy to suppress ovarian estrogen synthesis [38], the same would be true in premenopausal patients. However, recent data has cast doubt on this view [39]. Nevertheless, since all patients received the same endocrine regimen in the study, the choice of endocrine therapy is unlikely to have adversely influenced the study's results.

Overall, the results of the present study show that preoperative systemic therapy allows for a rapid ranking of antitumor activity of different treatments that can guide the development of new regimens in much larger and long-lasting randomized adjuvant studies. The prospective selection of patients with specific molecular characteristics of the tumor, such as the ER status in the ECTO II, allows for improving the sensitivity of the clinical test, and for the rapid discrimination of the beneficial applicability to specific subsets of patients.

Conclusion

Results of the ECTO II study of neoadjuvant anthracycline and taxane-containing chemotherapy confirmed the expected higher overall pCR rate in patients with ER− tumors compared with ER+ tumors. In both groups of patients, high rates of clinical response translated into a high proportion of patients being eligible for breast-conserving surgery. Of the three regimens evaluated, there was no clear 'winner' although the capecitabine-containing regimen AT→CMX, had the highest pCR rate in patients with ER+ tumors and met the pre-specified criteria for improvement over AT→CMF in this subgroup of patients. Translational studies investigating the interactions between therapeutic agents and tumor biology are warranted to explore the dependence of drug efficacy on ER status and other biological markers, and to enable treatment to be tailored to individual patients in future.

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Appendix: List of active ECTO II participating centers

Coordinating Center, Istituto Nazionale Tumori, Milano, Italy:, L. Gianni, M. Zambetti, E. De Benedictis
Ospedale Universitario S. Maria della Misericordia, Udine, Italy: M. Mansutti, G. Gentile
Hospital Vall d'Hebron, Barcelona, Spain: P. Gomez
Hospital Clinico Universitario de Valencia, Valencia, Spain: A. Lluch
Ludwig Boltzmann – Institute for Applied Cancer Research, Kaiser Franz Josef-Spital, Wien, Austria: C. Dittrich
Ospedale Policlinico S. Orsola Malpighi, Bologna, Italy: C. Zamagni
Hospital Universitario 12 de Octubre, Madrid, Spain: E. Ciruelos
Fondazione Salvatore Maugeri, Pavia, Italy: L. Pavesi
N.N. Petrov Research Institute of Oncology, St. Petersburg, Russian Federation: V. Semiglazov
Ospedale Civile di Camposampiero, Camposampiero, Italy: F. Gaion
Presidio Ospedaliero di Noale, Noale, Italy: M. Bari
Ospedale S. Bortolo, Vicenza, Italy: P. Morandi
Hospital de San Pau, Barcelona, Spain: B. Ojeda
Ospedale S. Giovanni Battista, Torino, Italy: M. Donadio
Hospital Arnau de Vilanova, Lleida, Spain: A. Llombart
Ospedale Civile di Legnano, Legnano, Italy: S. Fava
Frauenklinik vom Roten Kreuz, Munich, Germany: W. Eiermann
Istituto San Raffaele, Milano, Italy: E. Villa
Presidio Ospedaliero di Saronno, Saronno, Italy: C. Verusio
University Hospital Dr. Peset, Valencia, Spain: S. Olmos
Hospital Clíníco Universitario Lozano Bleza de Zaragoza, Zaragoza, Spain: R. Andrés
Medizinisches Zentrum, Ulm, Germany: C.Wolf
Istituto Valenciano de Oncologia, Valencia, Spain: M. A. Climent

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