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Estrogen receptor as the predictive factor for response to chemotherapy in breast cancer

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ABSTRACT

It has generally been accepted that breast cancer (BC) cells are equally responsive to chemotherapy (CHT) irrespective of ER status. However, subset analyses of disease outcome in recently reported trials on neoadjuvant and adjuvant CHT brought new information about the issue. The subject of this paper is to review these data and to communicate our own results. NSABP B27 was designed to evaluate if adding of docetaxel (D) to conventional neoadjuvant doxorubicin-cyclophosphamide (AC) CHT improves the clinical response rate (cRR) and pathological RR (pRR) in BC patients treated with 4 AC cycles only. Although the adding of D to AC CHT significantly improved RR in both ER-negative and ER-positive BC patients, the pCR was significantly higher in ER-negative than in ER-positive group (16.7% vs. 8.3%) irrespective which regimen was used. ECTO trial and several neoadjuvant studies confirmed the significantly inferior RR to neoadjuvant CHT in ER-positive compared to ER-negative BC patients. Three large randomized Cancer and Leukemia Group B (CALGB) studies (CALGB 8541, CALGB 9344, and CALGB 9741) compared the efficacy of different adjuvant anthracycline-containing or anthracycline/taxane-containing regimens in BC patients. The absolute benefit in 5-year disease-free survival in ER-negative and ER-positive BC patients treated with adjuvant CHT were 22.8% and 7.0%, while corresponding absolute benefits in overall survival were 16.7% and 4.0%. The concept of equal sensitivity of ER-negative and ER-positive BC to CHT has been changing. The future task is to find BC patients with ER-positive BC with no benefit from CHT in whom endocrine therapy is the therapy of first choice.

KEY WORDS: *Breast Neoplasms; Receptors, Estrogen; Antineoplastic Agents; Treatment Outcome; Chemotherapy, Adjuvant*

INTRODUCTION

Estrogen receptor (ER) have been recognized earlier as a weak prognostic factors (1), which means that women with ER-negative breast cancers (BC) have worse disease outcome without adjuvant systemic therapy in comparison to patients with ER-positive BC. Furthermore, ER is much powerful factor in predicting response to endocrine therapy: the larger the ER content within tumor cells, the higher the response to endocrine therapy (1). Because strong predictive value of ER and progesterone receptors (PgR) in response to endocrine therapy in BC is ultimately recognized, the St. Gallen guideline (2) uses steroid receptors (SR) as a discriminator between endocrine responsive and endocrine non-responsive BC. This discrimination had a substantial implication on the adjuvant systemic therapeutic approach.

Since ER-negative BC is insensitive to hormone therapy, chemotherapy (CHT) is a therapy of choice for these tumors. The relationship between ER content and response to chemotherapy has received little attention since it has been generally accepted that ER-positive and ER-negative breast tumor cells are equally responsive to CHT (1). The early results on influence of ER-status on CHT response in MBC patients were conflicting (3, 4). However, recent publications changed the common opinion about the benefit from CHT in ER-positive BC (5, 6), providing new data about less benefit from CHT, if at all, in patients with ER-positive BC. Because of these new findings, the subject of this paper is to comment them and communicate our own results about the predictive role of ER in response to CHT of BC.

THE RELATIONSHIP BETWEEN ER STATUS AND RESPONSE TO CHEMOTHERAPY IN NEOADJUVANT SETTING

Neoadjuvant or primary systemic CHT (PST) is indicated in locally advanced BC when shrinkage of the tumor and downstaging are warranted to allow tumor resection. As neoadjuvant chemotherapy does not prolong survival in patients with early BC (7), it is indicated only in those patients with large primary tumors to allow breast-conserving surgery. However, patients who achieved pathological complete remission (pCR) during PST have significantly longer disease-free survival (DFS) and overall survival (OS) compared to patients with partial remission (PR) or stable disease (SD) (7-10). Small tumor size and high proliferate activity (e.g. high Ki-67) are associated with better response to chemotherapy (11,12). Finally, the change of some biological markers, such as the change of Ki-67 expression during the first PST cycle (11) may serve as surrogate response predictor. Few studies investigate the association of ER with CHT response.

NSABP B27 was designed to evaluate if adding of docetaxel (D) to conventional neoadjuvant doxorubicin-cyclophosphamide (AC) CHT improves the clinical response rate (cRR) and pathological RR (pRR) in BC patients treated with 4 AC cycles only (6). Preliminary results confirmed that 4 cycles of preoperative docetaxel significantly increases the cRR and pRR when added to 4 cycles of AC CHT, irrespective of ER status. In ER-negative group AC+D and AC regimens achieved pCR in 22.8 % and 13.6% patients, respectively, while the corresponding results in ER-positive group were 14.1% and 5.7%, respectively.

However, the pCR was significantly higher in ER-negative than in ER-positive tumors (16.7% vs. 8.3%) irrespective which regimen was used. Although there was no report on menopausal status of included patients, more than 50% of women in all three treatment arms were younger than 50 years. This allow us to presume that substantial proportion of these women were premenopausal and speculate that the better RR in ER-positive patients receiving AC+D regimen compared to AC regimen could be a consequence of higher percentage of CHT induced amenorrhea with longer CHT duration (these data are also lacking). The influence of different duration of concomitantly given tamoxifen with CHT (24 vs. 12 weeks) might be another reason for observed difference between two patients' cohorts. Finally, ER-absent and ER-low expressive BC cohorts were merged in one group, which may blur the results of chemosensitivity in truly endocrine unresponsive BC patients (e.g. SR-absent tumors).

ECTO (13) trial analyzed the contribution of CMF to doxorubicine-paclitaxel (AT) PST in operable BC patients. They found that ER-negative tumors were significantly more responsive (more frequently associated with pCR) to doxorubicine-paclitaxel (AT) - CMF PST than ER-positive ones (odds ratio 7.8, p=0.0001) (13). Another analysis on a small number of patients (N=97) showed that ER-negativity and high Ki-67 proliferation index were the only two biological markers that predict better response to anthracycline-based PST. (14) However, none of biological markers studied (ER, Ki-67, HER-2) and pCR were not correlated with disease outcome (DFS and OS).

Buzdar AU et al (15) investigated the likelihood of response to anthracycline-based PST with or without taxanes as a function of ER status in 1292 BC patients. All patients received anthracycline-containing CHT with or without taxanes. Patients with SR-positive BC had significantly lower rates of pCR than ER-negative patients (P<0.001, Mantel-Haenszal test across treatments), regardless of type of regimen used or the duration of CHT. These results made authors to draw a conclusion about a necessity of defining in future trials relative efficacy of CHT vs. endocrine therapy in ER-positive BC.

Colleoni M et al (16) investigated the influence of SR content on the disease outcome in patients treated with PST. Patients with ER-absent/PgR-absent tumors had more than 4 fold greater chance of achieving pCR and 3.5 fold greater chance of having node-negative status after PST compared to patients with SR expressing BC. Conversely, higher incidence of pCR achieving in patients with SR-absent BC did not translate into a better DFS. Patients with pCR had non-significantly worse DFS than patients with non-pCR, while better DFS was significantly correlated with node-negative status after surgery. Multiple variant analyses found SRs to be the independent prognostic factors for DFS (women with SR-absent BC had significantly worse DFS). Women with SR expressive BC had additional benefit from endocrine therapy (ovarian function suppression in premenopausal and tamoxifen or aromatase inhibitors given as adjuvant endocrine therapy after surgery in postmenopausal women). This might also imply that SR-absent and SR-expressive BCs are two distinct biological entities, as has been suggested by gene profiling analysis (12).

However, in our small group of patients (N=90) with locally advanced BC (stage IIIA and IIIB) treated with 4 cycles of conventional FAC (5-FU-Doxorubicine-Cyclophosphamide) CHT, SR did not show significant correlation with RR, although there was a trend of being more node-negative patients with PgR absent tumors within a group with clinical response to chemotherapy (10). After a short FU period our results suggested significantly prolonged DFS and OS in patients to clinical objective response (cCR+cPR) compared with patients with cSD or cPD.

THE RELATIONSHIP BETWEEN ER STATUS AND RESPONSE TO CHEMOTHERAPY IN ADJUVANT SETTING

According to their investigation in node-positive premenopausal patients (n=1788) included in IBCSG trials I, II and VI, Colleoni et al reported that early initiation of adjuvant CHT may be beneficial for premenopausal women with ER-absent BC (17). The 10-year DFS in the CHT early-initiation (<21 days) group was 60% in contrast to 10-year DFS of 34% in CHT conventional-initiation (>21 days) group (HR, 0.49; 95%confidence interval [CI], 0.33 to 0.72; P=0.0003). The disease outcome was not affected by the timing of adjuvant CHT in premenopausal women with ER-expressing BC. The hypothesis that surgical removal of tumor increases angiogenesis (due to reduction of tumor-induced angiogenesis inhibitors) and enhance the growth of metastases has been reported earlier (18). The possible mechanism for the difference between ER-absent and ER-expressing BCs lies in the supposition that surgical trauma enhances the production of tumor growth factors such as transforming growth factor alfa (TGFα) which influence on high tumor proliferation may be enhanced by estrogen production (17). This is especially case in highly proliferating tumors such as those lacking ER. These are the reasons why early initiation of adjuvant CHT could be especially important in ER-absent BCs.

In another analysis Colleoni M et al correlated endocrine related factors (ER, PgR, age and menopausal status) with DFS in 1275 node-negative BC patients randomized to be treated with one cycle of perioperative CHT (commence within 36 hours after radical surgery) or no treatment. The results are somewhat different than the results reported in the previous study (19). After more than 13 years of follow-up period there was no difference in DFS between CHT treated and untreated premenopausal women. However, there was significantly higher 10-year DFS in postmenopausal women with ER-absent and/or PgR-absent BC between CHT treated and untreated groups (RR, 0.18; 95% CI, 0.06 to 0.49; P=0009) (19). The authors hypothesized that the response to adjuvant CHT is different in premenopausal and postmenopausal women possibly due to endocrine susceptibility for tumor-cell proliferation and response within substantial different endocrine environment between the two groups. Apart from direct cytotoxic effect, chemotherapy-induced amenorrhea is the second mechanism of action in premenopausal women with ER-positive BC. The probability of inducing amenorrhea is higher with longer duration of CHT. The lack of difference between CHT treated and untreated premenopausal women with ER-positive BC may be explained by the fact that one cycle of adjuvant CHT is insufficient to induce durable amenorrhea, while one cycle of adjuvant CHT is generally considered insufficient irrespective of ER status. There are conflicting results regarding the influence of estrogen production on the response to CHT in women with ER-negative BC (19). It seems that either the lack of estrogen or excessive amounts of estrogen increased proliferation of these tumors independently of estrogen binding to ER (19). One cycle of CHT in premenopausal woman may provoke rebound ovarian secretion of estrogen after temporary suppression, possible leading to estrogen-stimulated angiogenesis (19). According to this theory, prolonged ovarian suppression in premenopausal women with BC might be beneficial irrespective of SR status. On the contrary, CHT in postmenopausal women may substantially decrease estrogen production by adrenal gland, which could significantly improve disease outcome in these women with ER-negative BC (19).

IBCSG trial IX showed that adjuvant CHT did not provide additional benefit in node-negative postmenopausal women with ER-positive disease treated with tamoxifen (20). Five-year DFS for patients treated with 3 cycles of adjuvant CMF CHT followed by tamoxifen was 84% versus 86% for patients treated with tamoxifen alone. The corresponding 5-year OS for the two groups were 95% and 93%, respectively. On the contrary, adjuvant CMF had the significant impact on disease outcome (both for 5-year DFS and OS) in node-negative postmenopausal women with ER-negative BC. These results are in contrast with the results of the NSABP B-20 study (21) where node-negative ER-positive patients were randomized to receive 6 cycles of CMF or MF CHT plus tamoxifen vs. tamoxifen alone. At median follow-up period of 77 months, the subgroup analysis showed that CHT add a non-significant DFS benefit to tamoxifen in patients ≥ 50 years. These patients were not stratifield according to menopausal status thus allowing us to conclude that some percent of patient in 50-year older group were premenopausal or perimenopausal, in whom CHT induced secondary amenorrhea, leading to better DFS than tamoxifen alone.

The possible limitations of IBCSG IX trial are the duration of CHT (3 cycles) and non-anthracycline regimen used (22). To date there is one study suggesting that in low-risk patients

(node-negative women over 40 with ER-positive BC) 3 cycles of adjuvant CMF CHT exerts the same effect as 6 cycles of the same adjuvant CHT (23). Recent EBCTCG analysis (24) did not show significant benefit with longer duration of adjuvant CMF CHT (6 vs. 9 vs. 12 months). Indirect comparison of adjuvant CMF-based and anthracycline-based CHT did not show significant differences in relative risk reduction in disease relapse and BC mortality (24). However, direct comparison of these two adjuvant CHT regimens (14000 included women) showed significant reduction in both BC recurrence and mortality with anthracycline-containing CHT (recurrence rate ratio 0.89 [SE 0.03], 2p=0.001; breast cancer death rate ratio 0.84 [SE 0.03], 2p=0.00001). Furthermore, anthracycline-based regimens reduced the mortality rate by 20% in women older than 50 years, irrespective of ER status. (24)

The added benefit of anthracycline-based CHT was studied in a group of postmenopausal patients with either axillary node involvement or histological grade 2 or 3 tumors (25). Eight hundred and thirty five patients were randomized to receive CHT and tamoxifen or tamoxifen only. Benefit of CHT was the greatest in ER-negative group, while in patients with ER-rich BC there was no added benefit of CHT over tamoxifen. Large SWOG 8814 (INT0100) trial (26) showed that adjuvant CAF CHT added significant benefit to tamoxifen in comparison to tamoxifen alone in node-positive postmenopausal patients with ER-positive BC, especially when tamoxifen was given sequentially to CHT (10-year DFS and OS adjusted ratio were 1.31 and 1.21 for tamoxifen vs. CAF CHT + tamoxifen). However, the biomarker analyses identified the subsets of patients with no CHT benefit: BC with high ER content, low-intermediate histological tumor grade and HER2-negative BC in a group with 1-3 involved axillary lymph nodes.

French authors analyzed the results of 8 French Adjuvant Study Group (FASG) trials with 3233 included patients receiving epirubicin-based CHT (27), endocrine therapy (LHRH agonist and/or tamoxifen), combined CHT and endocrine therapy, or no adjuvant therapy (27). The patients were divided into 4 groups according to ER/PgR status. The results revealed that SR subgroups did not influence the risk of relapse. There were no differences in 9-year DFS between adjuvant CHT group and group without adjuvant therapy despite SR status. The 9-year DFS in patients with ER-positive/PgR-positive groups were 51% for CHT group, 70% for endocrine therapy group and 73% for the combination of CHT and endocrine therapy.

Recently reported intent-to-treat analysis on the influence of adjuvant CHT on anastrozole effect in ATAC trial among more than 6200 postmenopausal patients randomized to receive adjuvant anastrozole or adjuvant tamoxifen, revealed that, at 68-month follow up period, there is no potential treatment interaction with CHT (28). This means that the relative benefit of anastrozole over tamoxifen did not significantly differ between patients who received CHT and those who did not (HR, 0.89 vs. 0.74 for those with or without prior chemotherapy, respectively; $P = 0.21$ for interaction). The median age of included patients was about 65 years, 84% patients had ER-positive BC and 22% of patients received adjuvant CHT (CMF-, anthracycline-, or taxane-based CHT).

One recently published paper analyzed the data of 3 CALGB trials (CALGB 8541, CALGB 9344, CALGB 9741) investigating the outcome (DFS and OS) of adjuvant chemotherapy according to ER-status (5). All patients with ER-positive disease included into this comparison received adjuvant tamoxifen. In CALGB 8541 study 1550 patients were randomized into three arms with escalating doses of adjuvant FAC CHT: low-dose CHT consisting of 4 cycles cyclophosphamide 300 mg/m^2, doxorubicin 30 mg/m^2, fluorouracil 300 mg/m^2, moderate dose CHT consisting of 6 cycles of cyclophosphamide 400 mg/m^2, doxorubicin 40 mg/m^2 and fluorouracil 400 mg/m^2 and high dose CHT consisting of 4 cycles of cyclophosphamide 600 mg/m^2, doxorubicin 60 mg/m^2 and fluorouracil 600 mg/m^2. Patients in the high and moderate dose arms received the same total dose, while patients included in low dose arm received the half of that dose. Comparing benefits of high over low dose regimen, absolute improvements in DFS and OS for ER-negative BC patients were 13.9% and 6.6%, and for patients with ER-positive BC were 6.6% and 4%. CALGB 9344 study had 3 x 2 factorial design with 3121 enrolled women. First randomization included three treatment arms with escalating doxorubicin dose (60, 75 and 90 mg/m^2) in AC combination with fixed dose of cyclophosphamide of 600 mg/m^2. After 4 cycles of AC CHT patients undertook the second randomization: to receive additional 4 cycles of 3-weekly scheduled paclitaxel of 175 mg/m^2 or no further treatment. Results did not confirm that the escalation of doxorubicin derived additional benefit. The absolute DFS and OS benefit of adding paclitaxel to standard AC adjuvant regimen for patients with ER-negative BC were 8.2% and 7.4%, while for patients with ER-positive BC were 2,1% and 0%.

CALGB 9741 trial was of 2x2 factorial design with the first randomization between two treatment schedules: 2-weekly regimen and 3-weekly regimen, and the second randomization with sequential and concurrent therapy that contained doxorubicin, cyclophosphamide and paclitaxel in standard doses. Patients receiving dose-dense CHT had significantly better disease outcome despite how the drugs were delivered, concomitantly or sequentially. The benefits in DFS and OS for women with ER-negative BC in dose-dense regimen group were 9.1% and 7.4%. However, for women with ER-positive tumors the absolute benefit for DFS was 2.8, while there was no survival advantage for these women. Overall, the absolute benefit for DFS and OS between low-dose regimen in CALGB 8541 and 2-weekly scheduled CHT in CALGB 9741 for ER-negative patients were 22.8% and 16.7%, respectively, and for ER-positive patients were 7% and 4%.

The pattern of relapse was similar across all three studies: ER-negative BC tended to relapse within the first 2-3 years, while relapse rate in the first few years in patients with ER-positive tumors treated with adjuvant tamoxifen were low. However, the pattern of relapse in patients with ER-positive BC not treated with adjuvant tamoxifen is the same as of the patients with ER-negative tumors, suggesting the early positive effect of tamoxifen on reduction of disease progression in ER-positive BC (5). The relative benefit of adjuvant CHT in ER-negative BC group is the greatest in the first (55%) and the second (33%) year after surgery. This risk reduction probably is the same in ER-positive group. However, as the baseline risk for relapse is greater in patients with ER-negative BC, the absolute benefit of CHT is also greater in these women than in patients with ER-positive tumors. The authors conclude that with more effective endocrine therapy, the benefit of adjuvant CHT might not be statistically detectable.

We evaluated a group of 482 early breast cancer patients, diagnosed from 1986 to 1994, who were treated either with adjuvant CMF CHT, or adjuvant endocrine therapy [ovarian ablation (OA) by irradiation for premenopausal, or tamoxifen for postmenopausal women] (29). All patients were either node negative with grade 3 BC, or had 1-3 positive nodes regardless of tumor grade. A group of patients with SR-positive tumors defined as ER-positive/PgR-positive, ER-positive/PgR-negative, and ER-negative/PgR-positive were separated and divided according to menopausal status. Among these premenopausal (N=166) and postmenopausal (N=172) women DFS and OS were compared between women treated with adjuvant CHT and adjuvant endocrine therapy. There was no difference in DFS and OS between premenopausal women treated with adjuvant CHT and those treated with adjuvant OA. However, significantly more postmenopausal patients, treated with adjuvant CHT, developed disease relapse comparing to postmenopausal women treated with adjuvant tamoxifen (Chi-square test, p<0.001), with local recurrences and bone metastases occurring significantly more frequently (Chi square tests, p=0.01, p=0.006, respectively). Furthermore, postmenopausal women treated with adjuvant CHT had significantly worse DFS (Log rank test, p=0.013) compared to tamoxifen group, while there was no difference in OS between the two groups. The lack of difference between premenopausal women with SR-positive BC may be attributable to CHT-induced permanent amenorrhea in patients treated with CHT. Although the relevant data are lacking, we can assume that in majority of those women CHT did induced durable amenorrhea, since the their median age was 44 years (range 34-53 years). However, there was no endocrine effect of adjuvant CHT in postmenopausal women, which may be the cause of worse DFS in these women. OS was not affected possibly because the majority of these women were treated with tamoxifen upon disease relapse.

We also investigate the influence of SR status on disease outcome in grade 3 BC node

negative and 1-3 node positive BC patients treated with adjuvant CMF CHT (N=161) (30). Significantly better DFS was found in node-negative group in patients with ER-negative/ PgR-negative BC in comparison with ER-positive and/or PgR-positive patients. However, the only significant predictor of disease outcome was node status. Of interest is that women under 40 with SR-positive BC had a trend towards worse DFS (log rank test, p=0.054) compared to women over 40 with SR-positive BC, which indicate the probable influence of CHT-induced amenorrhea on disease outcome in the letter group.

CONCLUSION

Although there are limited data on the relationship between ER status and response to CHT, we have enough evidence to conclude that ER-absent and ER-expressive BC are two distinct diseases with different prognosis and different sensitivity to chemotherapy and endocrine therapy, as well. The future task is to identify those ER-positive patients who derive the significant benefit of CHT and those with no such benefit, in whom endocrine therapy is the therapy of first choice.

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