Pregnancy-associated breast cancer is as chemo-sensitive as non-pregnancy-associated breast cancer in the neoadjuvant setting

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Background: The aim of this study was to determine the chemosensitivity of pregnancy-associated breast cancer (PABC) in the neoadjuvant setting by comparing the observed pathological complete response (pCR) rate with the rate predicted by a validated nomogram.

Methods: Data from 48 PABC patients who received neoadjuvant chemotherapy (NACT) were collected. To predict the response rate to chemotherapy, we used well-calibrated logistic regression-based nomograms to calculate individual probability of pCR.

Results: Observed rates of pCR were concordant with predictions in the whole sample and in the analyzed subgroups. For the whole sample, the area under the receiver-operated curve (AUC) was 0.77 (95% CI 0.66–0.87). The calibration of predicted and observed probabilities was excellent. In the subgroup analyses (NACT initiated during pregnancy or postpartum, NACT with only anthracycline or both anthracycline and taxanes), discriminations assessed by AUC were significantly above 0.5, except for patients treated with anthracycline only. The interpretation was limited by a lack of power.

Conclusion: Through the use of nomograms, our study demonstrates that PABC is as chemosensitive as non-PABC and suggests that taxanes should be part of the NACT regimen for PABC. Further studies are warranted to increase the power of the presented data.

Key words: breast, cancer, chemotherapy, neoadjuvant, nomogram, pregnancy

introduction

Pregnancy-associated breast cancer (PABC) is defined as breast cancer diagnosed during pregnancy or within 1 year of delivery. It accounts for 8% of breast cancer cases occurring in women younger than 45 years of age [1]. PABC has been reported to have specific phenotypes such as low hormone receptor positivity and a high rate of HER2 overexpression [2, 3]. This breast cancer is described as being particularly aggressive and having a worse prognosis than non-PABC [4]. PABC may actually be several different diseases, such as breast cancers that are closely related to pregnancy in their oncogenesis as well as breast cancers that are completely independent of pregnancy. An improvement in the understanding of PABC may help to differentiate these entities and distinguish their chemosensitivities. However, the chemosensitivity of PABC is not well known and there is frequently a delay in diagnosis. The tumor size of these breast cancers has been reported to be greater than that of non-PABCs [5, 6]. Neoadjuvant chemotherapy (NACT) is therefore an option for PABC, and anthracycline-based regimens have been considered safe during pregnancy [7–9]. Complete pathological eradication of the invasive cancer, the pathological complete response (pCR), reveals chemosensitivity because it provides a powerful early surrogate for long-term survival and is considered an indicator of benefit from chemotherapy [10]. We previously developed a clinical pathological variable-based on the NACT response prediction model [11]. This model was built using data from patients who received preoperative NACT so that tumor response to treatment could be measured directly. Our response prediction nomogram was subsequently validated on two sets of independent cases from two different institutions.

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different than from the training cohorts and proven to be accurate [12]. This tool can be used to compare theoretical and observed pCR rates in a specific sample, thus providing a multivariate stratification for maximizing the accuracy of estimation. In this study, we investigated the chemosensitivity of PABC in the neoadjuvant setting by comparing the theoretical pCR rate given by a validated nomogram with the observed pCR rate.

**Methods**

**Study Population**

From January 2000 to December 2008, data from 57 patients with PABC who received NACT were collected in three databases. Patient data came from Institut Gustave Rousy, Tenon Hospital, and Cochin. Immunohistochemical data and grades were missing for nine patients, so only 48 patients were included in this analysis; 11 patients received at least one course of chemotherapy during pregnancy [mean number of cycles carried out during pregnancy: 3.1 (range: 1–5)], and 37 patients received all courses after delivery, either because delivery was induced or because breast cancer was diagnosed after delivery. Table 1 describes the characteristics of the sample. Details regarding tumor staging were recorded according to the International Union Against Cancer TNM (tumor–node–metastasis) staging system [13]. Patients were classified as having inflammatory breast carcinoma if they presented with clinical inflammatory signs in the breast (diffuse or local induration of the skin with erythema) or if the histopathologic examination demonstrated the invasion of dermal lymphatics. The analyzed features included age, histologic type, histopathologic examination demonstrated the invasion of dermal lymphatics. The analyzed features included age, histologic type, histopathologic examination demonstrated the invasion of dermal lymphatics. The analyzed features included age, histologic type, histopathologic examination demonstrated the invasion of dermal lymphatics.

**Mathematical and statistical analysis.** To evaluate the theoretical response rate to chemotherapy, we used well-calibrated logistic regression-based nomograms that we previously developed and published [12, 15]. We built these models in training cohorts and validated them in independent cohorts from centers other than the training cohort. We tested clinicopathological characteristics (age, tumor size, nodal status, histologic type and grade, estrogen receptor status, multifocality, and number of courses of preoperative chemotherapy) in a multivariate analysis for associations with pCR. We then developed interfaces to calculate the individual probabilities of pCR in patients with PABC using the nomograms and the pCR rates observed. We then developed interfaces to calculate the individual probabilities of pCR in patients with PABC using the nomograms and the pCR rates observed.

We used two parameters to determine whether PABC was as chemosensitive as non-PABC: discrimination and calibration [16]. Discrimination (i.e., whether the relative rankings of individual predictions were in the correct order) was quantified with the area under the receiver-operating characteristic curve (AUC). The AUC is identical to the concordance index and ranged from 0 to 1 (1 indicating perfect concordance, 0.5 indicating no association, and 0 indicating perfect discordance). Confidence intervals were calculated using a bias-corrected bootstrap with 1000 iterations. Calibration corresponds to the agreement between the observed outcome frequencies and the predicted probabilities. The results are displayed in a calibration graph that shows the relationship between the observed outcome frequencies and the predicted probabilities for two groups of patients categorized according to a median split (semi-cohorts with the lowest/highest predicted pCR rate). A calibration curve can be approximated by a regression line with the intercept \( \alpha \) and slope \( \beta \). These parameters can be estimated in a linear regression model with the event as the outcome and the linear predictor as the only covariate. Well-calibrated models have \( \alpha = 0 \) and \( \beta = 1 \) [ideal line: intercept at (0,0), slope: 45°]. Therefore, a sensible measure of calibration (the unreliability index) is a likelihood ratio statistic testing the null hypothesis that \( \alpha = 0 \) and \( \beta = 1 \). The statistic has a \( \chi^2 \) distribution with 2 df. To calculate the power of this test (necessary to estimate sample size effect), we

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<th>Table 1. Patient characteristics</th>
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Values are given as \( n \) (%), unless otherwise specified. CT, chemotherapy; pCR, pathological complete response; SBR grade, Scarff Bloom Richardson grade.
considered that individual predictions of pCR rates were constant as the null hypothesis.

This study was conducted according to institutional and ethical rules of research. All analyses were carried out using the R package with the Design, Hmisc, and Verification libraries (http://lib.stat.cmu.edu/R/CRAN/).

results

The study included 57 patients who received four courses of anthracycline-based chemotherapy or four courses of anthracycline-based chemotherapy followed by four courses of paclitaxel, but since data were missing for nine patients, only 48 patients were included in the analysis. Among them, 10 had pCR (no residual disease in the breast and nodes). Twenty-two patients (46%) had metastatic nodes at surgery. We calculated the individual probability of pCR in response to neoadjuvant treatment with specific nomograms corresponding to the chemotherapy regimen administered.

Overall, as reported in Table 2, the observed rates of pCR were concordant with predictions in the whole sample and in the subgroups that were analyzed: (i) discriminations assessed by AUC were significantly above 0.5, except for patients who were not treated with neoadjuvant taxanes, and (ii) calibration curves were satisfactory. Unreliability indexes were not significant.

discrimination of probability of pCR to NACT in the whole sample

For the whole sample, the observed rates were in accordance with predictions, as demonstrated by discrimination and calibration.

Discrimination. In the original training set, the AUC obtained with the logistic regression model was 0.77 (95% CI 0.74–0.80). This means that given two randomly selected patients, the patient with the worse outcome was predicted to have a worse outcome in 77% of possible pairs with discordant outcome. In this study population, including only PABC, the AUC for the logistic regression model was significant at 0.77 (95% CI 0.66–0.87). The receiver-operating characteristic (ROC) curve is reported in Figure 1.

Calibration. The calibration of the nomograms to predict pCR in PABC is reported in Figure 2. In this figure, patients were separated into two subgroups according to their predicted probability of pCR (x-axis). The observed pCR rate at histopathologic examination is reported on the y-axis. Perfect predictions are plotted on the ideal line: intercept at (0,0), slope: 45°. The predicted probability and observed proportion of pCR of patients with the lowest predicted pCR were 7% and 8%, respectively. The predicted probability and observed proportion of pCR of patients with the highest predicted pCR were 35% and 33%, respectively. The differences between predictions and observations were not significant ($P = 0.76$, power = 0.91).

Thus, using a nomogram developed to predict pCR for women with non-PABC provided accurate predictions for women with PABC. We deduce from this finding that PABCs are as chemosensitive as non-PABCs.

progression under NACT

One of the main risks of NACT is progression during treatment, so we specifically recorded the occurrence of this phenomenon. Three patients clinically progressed under chemotherapy and two of them required a strategic change. This number is in accordance with previous reports.

prediction of probability of pCR to NACT in PABC according to the onset of chemotherapy

We evaluated whether there were differences in discrimination and calibration if the onset of NACT was during pregnancy versus after delivery (Table 2).

| Table 2. Predicted probability of pCR according to the nomogram and the percentage observed for the whole sample and for subgroups |
|---|---|---|---|---|
| N | Predicted probability of pCR according to the nomogram (%) | Percentage observed (%) | Calibration, $\alpha$ (±SE); $\beta$ (±SE); $P$ value of the unreliability index* | Discrimination, area under the ROC curve, $P$ value |
| Whole sample | 48 | 21 | 21 | $\alpha = -0.03 \pm 0.01$; $\beta = 1.1 \pm 0.3$; $P = 0.76$ | AUC = 0.77; $P = 0.005$ |
| NACT administered | 11 | 22 | 18 | $\alpha = -0.1 \pm 0.15$; $\beta = 1.3 \pm 0.5$; $P = 0.29$ | AUC = 0.94; $P = 0.04$ |
| NACT administered postpartum | 37 | 21 | 22 | $\alpha = 0.0 \pm 0.1$; $\beta = 1.0 \pm 0.4$; $P = 0.51$ | AUC = 0.71; $P = 0.04$ |
| Anthracycline only | 25 | 19 | 12 | $\alpha = 0.1 \pm 0.13$; $\beta = 0.2 \pm 0.6$; $P = 0.15$ | AUC = 0.59; $P = 0.32$ |
| Anthracycline + taxanes | 23 | 24 | 30 | $\alpha = -0.01 \pm 0.12$; $\beta = 1.3 \pm 0.4$; $P = 0.07$ | AUC = 0.84; $P = 0.005$ |

* A calibration curve can be approximated by a regression line with intercept $\alpha$ and slope $\beta$. The unreliability index tests the null hypothesis that $\alpha = 0$ and $\beta = 1$ and is correct if not significant.

AUC, area under the curve; NACT, neoadjuvant chemotherapy; pCR, pathologic complete response; ROC, receiver-operating characteristic; SE, standard error.
the AUC of predictions using nomograms was 0.71 (95% CI 0.59–0.84).

Calibration. The calibration of the nomograms to predict pCR in PABC according to the onset of chemotherapy is reported in Figure 3. There was no significant difference between predicted probabilities and observed proportions, regardless of the onset of chemotherapy (Ps = 0.29 and 0.51 for chemotherapy started during pregnancy and after delivery, respectively; power 0.32 and 0.8, respectively).

Prediction of probability of pCR to NACT in PABC according to the use of taxanes

We evaluated whether there were differences in pCR rates according to the regimen administered (taxane or no taxanes) (Table 2).

Discrimination. For patients who received only anthracyclines without taxanes, the AUC was 0.59 (95% CI 0.37–0.81). Therefore, the discrimination in this sample was insufficient. For patients treated with neoadjuvant anthracyclines and taxanes, the AUC was 0.84 (95% CI 0.74–0.93).

Calibration. The calibration of the nomograms to predict pCR in PABC according to the chemotherapy regimen administered is reported in Figure 4. The calibration of the prediction was average for patients treated only with neoadjuvant anthracyclines. The observed pCR rate was less than the expected pCR rate according to individual predictions based on patient characteristics. The calibration curve was poorly calibrated. The P value of the unreliability index did not reach significance (0.15), but there was a lack of power due to the sample size (power = 0.70). This means that some cases of PABC are less likely to be chemosensitive to anthracycline-only NACT compared with non-PABC cases. Combined with the poor discrimination, this suggests that anthracycline-only NACT is not optimal for the treatment of PABC. The calibration of the logistic regression model was excellent for patients treated with neoadjuvant anthracycline plus taxanes (P = 0.7). For patients with the highest predicted pCR to anthracycline plus taxane-based NACT, the rate of pCR
was above the expectation (+12%). This indicates that patients with PABC should receive NACT with anthracyclines and taxanes.

discussion

According to international recommendations, the treatment of PABC should adhere closely to standardized protocols for patients without concomitant pregnancy [17]. However, PABC may have specific characteristics, as its pathogenic pathway is probably different from that of non-PABC [18, 19].

If chemotherapy can be administered during pregnancy, the choice of the neoadjuvant setting remains a strategic one with the risk (even if low) of disease progression. The particular characteristics of PABC and pharmacokinetic changes that occur in pregnancy, such as alterations in plasma volume distribution, may impact chemosensitivity [20]. Preoperative chemotherapy, initially used only for locally advanced breast cancer, has become more common for patients with operable disease [21]. Achieving pCR is a strong independent predictor of disease-free state and overall survival for patients with breast cancer, and it is considered a surrogate marker of chemosensitivity [22, 23]. We investigated the chemosensitivity of PABC because there is a lack of evidence in the literature suggesting that the behavior of these particular cancers is similar to non-PABC. To our knowledge, this question has never been addressed. The most important studies have reported the safety of anthracycline-based chemotherapy, but few patients had actually received NACT [7, 9, 24]. In the largest series reported by Hahn et al. [25], 25 patients received NACT and had a pCR rate of 32%. Our results confirm this study and support a neoadjuvant strategy for treating PABC. Our results suggest that PABC patients should receive taxanes as part of their regimen because the chemosensitivity to a regimen based only on anthracyclines is insufficient, while adding taxanes results in a better chemosensitivity compared with non-PABC cases. A recent review of the literature showed a favorable toxicity profile of taxanes during the second and third trimesters of pregnancy, and these results are supported by pharmacological evidence [26].

Figure 4. Calibration of the nomogram to predict pCR in the PABC sample treated with anthracycline-based NACT only (•, grouped observations; †, number of cases) or with NACT including both anthracyclines and taxanes (Δ, grouped observations; †, number of cases).
and distinguish their chemosensitivities. Further studies are warranted to increase the power of the data presented in our study.

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**disclosure**

The authors have declared no conflicts of interest.

**references**