Clinical benefit from neoadjuvant chemotherapy in oestrogen receptor-positive invasive ductal and lobular carcinomas

Y Delpech, C Coutant, L Hsu, E Barranger, T Iwamoto, C H Barcenas, G N Hortobagyi, R Rouzier, F J Esteva and L Pusztai

Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; Department of Gynecology and Obstetrics, Lariboisiere Hospital, AP-HP, Paris, France; Department of Surgical Oncology, Georges Francois Leclerc Cancer Center, Dijon, France; Department of Hematology and Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; Department of Gynecology and Obstetrics, Tenon Hospital, AP-HP, Paris, France and Section of Breast Medical Oncology, Yale Cancer Center, Yale School of Medicine, 333 Cedar Street, PO Box 208032, New Haven, CT 06520-8028, USA

Background: The aim of this study was to compare clinical and pathological outcomes after neoadjuvant chemotherapy between oestrogen receptor (ER)-positive invasive pure lobular carcinoma (ILC) and invasive ductal carcinoma (IDC).

Methods: This analysis included 1895 patients (n = 177 ILC; n = 1718 IDC), with stage I–III breast cancer, who received neoadjuvant chemotherapy. Clinical and pathological response rates, the frequency of positive surgical margins and rate of breast-conserving surgery were compared.

Results: There was a trend for fewer good clinical responses in ILC compared with IDC. Tumour downstaging was significantly less frequent in ILC. Positive or close surgical resection margins were more frequent in ILC, and breast-conserving surgery was less common (P < 0.001). These outcome differences remained significant in multivariate analysis, including tumour size, nodal status, age, grade and type of chemotherapy. Invasive pure lobular carcinoma was also associated with a significantly lower pathological complete response (pCR) rate in univariate analysis, but this was no longer significant after adjusting for tumour size and grade.

Conclusion: Neoadjuvant chemotherapy results in lower rates of clinical benefit, including less downstaging, more positive margins and fewer breast-conserving surgeries in ER-positive ILC compared with ER-positive IDC. Pathological complete responses are rare in both groups, but do not significantly differ after adjusting for other variables.

Pure invasive lobular carcinomas (ILCs) account for 10–15% of all breast cancers and are almost invariably oestrogen receptor (ER)-positive and tend to have low histological grades (grades I and II) (Fisher et al., 1975; Wellings et al., 1975; World Health Organisation, 1982). Invasive pure lobular carcinoma is characterised by small, round cells with scant cytoplasm that infiltrate the stroma in single files, which makes it more difficult to palpate or detect this type of cancer with mammogram (Katz et al, 2007). This histological feature may also lead to higher rates of positive surgical margins after breast-conserving surgery (Porter et al, 1999; Molland et al, 2004; Waljee et al, 2008; Boughey et al, 2009). The rates of pathological complete response (pCR) to neoadjuvant chemotherapy are also significantly lower in ILC compared with invasive ductal carcinomas (IDCs) (Cristofanilli et al, 2005). Several investigators have suggested that ILC histology is a relative contraindication for preoperative chemotherapy because the expected benefit is modest because of less frequent clinical responses, low pCR rates and more frequent positive surgical

*Correspondence: Professor L Pusztai; E-mail: lajos.pusztai@yale.edu

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Comparing outcomes between ILC and IDC in general has substantial limitations because of the uneven distribution of confounders, including histological grade and ER status between these two distinct histological subtypes. The question whether histology itself, after adjusting for differences in grade and ER, remains a predictor of lower response rates and higher rates of positive margins remain controversial. Previous studies performed multivariate analysis to address this question and most results suggested that histology remains an important independent factor. However, Boughey et al. (2009) and Wagner et al. (2009) reported frequent clinical responses in ILCs to preoperative chemotherapy and margin positivity rates after breast-conserving surgery were similar between patients who received neoadjuvant chemotherapy and those who did not. In this study, we compare rates of pathological response, surgical margin status and rates of breast-conserving surgery between ER-positive ILC and IDC that received neoadjuvant chemotherapy. We excluded ER-negative tumours from the analysis to eliminate an important confounder.

PATIENTS AND METHODS

Patient population. Patients were identified for this study from a prospectively maintained clinical database of the University of Texas MD Anderson Cancer Centre. Patients were selected for inclusion if they had ER-positive stage I–III breast cancer diagnosed between 1990 and 2010 and received neoadjuvant chemotherapy. This search initially identified 2592 patients. After reviewing the medical records, the following patients were excluded: male breast cancer (n = 12), patients with axillary metastasis without an identifiable primary breast tumour (n = 13), metastatic disease at diagnosis (n = 13), patients who received neoadjuvant chemotherapy alone (n = 10) or underwent partial excisional biopsy before neoadjuvant chemotherapy (n = 214). We also excluded patients with rare or mixed histological subtypes (n = 224) to focus on the comparison of pure lobular vs pure ductal carcinomas. Patients with overexpression of human epidermal growth factor receptor-2 (HER2) were also included. Review of medical records also revealed miscoding of ER and progesterone receptor (PR) results in 21 patients who had hormone receptor-negative breast cancer and in 189 patients who received neoadjuvant endocrine therapy alone. The patient population used for this study included 1895 patients who had hormone receptor-negative breast cancer and in whom hormone receptor status was determined using immunohistochemistry or gene amplification by FISH. PR and HER2 measurements (World Health Organisation, 1982). Oestrogen receptor and PR positivity were defined as nuclear staining ≥10% and HER2 positivity was defined as 3+ staining on immunohistochemistry or gene amplification by FISH. Histological grade was assessed following the modified Black’s nuclear grading system.

After completion of neoadjuvant chemotherapy, 1827 (96.4%) patients underwent primary breast surgery and 1826 (96.5%) had axillary lymph node staging (level I and II dissection or sentinel lymph node biopsy). If invasive or in situ carcinomas were seen within 2 mm of the surgical margin on microscopic examination (i.e. positive or close tumour margins), a second operation was performed to achieve clear margins. Pathological complete response was defined as no evidence of invasive carcinoma in the breast and axillary lymph nodes.

Statistical analysis. The $\chi^2$ test (or Fisher’s exact test when the sample size was small) was used to evaluate associations between categorical variables and histological subtype. The Student’s t-test was used for continuous variables. We also performed stratified analysis by histological grade (grade I/II vs III). Univariate logistic regressions were performed, including histological subtype, nuclear grade, nodal status tumour size, multifocality, age, race, menopausal status, HER2 status, Ki-67 score and the type of neoadjuvant chemotherapy as variables to identify predictors of breast-conserving therapy, positive margins and pCR. From this model, an odds ratio (OR) for each variable was determined with a 95% confidence interval (CI). All significant variables from the univariate analysis were included in a subsequent multivariate analysis. Median overall survival and distant disease-free survival were determined using the Kaplan–Meier methods. All analyses were performed using R package with Survival, Design, Hmisc, Rpart and Lexis libraries (http://lib.stat.cmu.edu//R/CRAN/).

RESULTS

Patient characteristics are summarised in Table 1: 177 patients had ILC (9%), and 1718 patients had IDC (91%). Patients with ILC were older, had larger and lower grade (grades I/II) tumours and had fewer HER2-positive cancers compared with IDC. Anthracycline-based or taxane and anthracycline combination regimens were used equally frequently in both histological groups, but trastuzumab use was more common in IDC (Table 1).

Significant downstaging was observed in both histological types ($P < 0.0001$) (Supplementary Figure 2A), but it was more common among IDC. Forty-one per cent of ILCs had lower tumour stage after neoadjuvant chemotherapy compared with baseline, whereas similar downstaging occurred in 64% of IDCs ($P < 0.0001$) (Supplementary Figure 2B).

Positive or close surgical resection margins were significantly more frequent in ILC patients (19 vs 11%; $P = 0.0001$) and this remained significant even after multivariate analysis, including tumour size and grade (OR = 1.82; 95% CI, 1.13–2.93; $P = 0.01$). At the end, breast-conserving surgery was less frequent in ILC patients than in IDC patients (19 vs 34%; $P < 0.001$) (Table 2) and histology remained an independent predictor of mastectomy (OR = 1.86; 95% CI, 1.15–2.99; $P = 0.01$) even after adjusting for age, tumour grade, initial tumour size, multifocality, nodal status and clinical stage (Table 3).

Invasive lobular histology was also associated with significantly lower pCR rates (3.5 vs 14%; $P < 0.001$) (Table 2). In univariate analysis, multifocal tumour, higher tumour size, node-positive status and lower nuclear grade were also significantly associated with lower pCR rates. In multivariate analysis, including the above variables, histology was no longer significant (Table 4). Similarly, in an analysis stratified by grade, pCR rates were no longer

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Table 1. Patient demographic and treatment clinical characteristics

| Demographic or clinical characteristics | ILC (n = 177) | IDC (n = 1718) | \( \chi^2 \) P-value |
|----------------------------------------|-------------|--------------|------------------|
| No. of patients | % | No. of patients | % |
| Age (years) | | | |
| Median | 54 | 50 | <0.001 |
| Range | 35–62 | 21–83 | |
| Race | | | |
| Asian | 6 | 3 | 96 | 6 | 0.51 |
| Black | 19 | 11 | 223 | 13 | |
| White | 150 | 85 | 1375 | 80 | |
| Other | 2 | 1 | 24 | 1 | |
| Menopausal status | | | |
| Yes | 114 | 64 | 899 | 52 | 0.003 |
| Concurrent bilateral breast cancer | | | |
| Yes | 16 | 9 | 74 | 4 | 0.008 |
| Tumour size (cm) | | | |
| Median | 4.5 | 3.4 | <0.001 |
| Range | 0.4–12 | 0.4–20 | |
| Multifocal tumour | | | |
| Yes | 42 | 24 | 326 | 19 | 0.1 |
| T stage | | | |
| T1–2 | 99 | 56 | 1187 | 69 | <0.001 |
| T3–4 | 78 | 44 | 529 | 31 | |
| N stage | | | |
| N1 or sup | 102 | 58 | 1089 | 63 | 0.15 |
| AJCC stage | | | |
| I/II | 111 | 63 | 1076 | 63 | 0.94 |
| III/IV | 66 | 37 | 641 | 37 | |
| HER2 status | | | |
| Negative | 84 | 47 | 793 | 46 | 0.006 |
| Positive | 13 | 7 | 288 | 17 | |
| Nuclear grade | | | |
| I–II | 145 | 82 | 722 | 42 | <0.001 |
| III | 24 | 14 | 980 | 57 | |
| Ki-67 score* | | | |
| <20 | 48 | 27 | 224 | 13 | <0.001 |
| >20 | 28 | 16 | 518 | 30 | |
| Neoadjuvant chemotherapy regimenb | | | |
| Anthracycline and taxane based | 137 | 77 | 1378 | 80 | 0.4 |
| Anthracyline-based only | 27 | 15 | 209 | 12 | 0.5 |
| Taxane-based only | 13 | 7 | 124 | 7 | 1 |
| Trastuzumab | 9 | 5 | 254 | 15 | <0.001 |
| Neoadjuvant hormonotherapy in combination with chemotherapy | 3 | 2 | 54 | 3 | 0.4 |
| Adjuvant chemotherpay | 32 | 18 | 419 | 24 | 0.07 |
| Adjuvant hormonotherapy | 146 | 82 | 1382 | 80 | 0.6 |
| Adjuvant radiotherapy | 146 | 82 | 1311 | 76 | 0.08 |

Abbreviations: A = adriamycin; AJCC = American Joint Committee on Cancer; C = cyclophosphamide; E = epirubicin; F = 5-fluorouracil; H = herceptin; HER2 = human epidermal growth factor receptor 2; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; T = taxane.

*Ki-67 score were available in 76 patients in ILC group and in 742 IDC group.

bThe most common regimen consisted of T, F, A or E and C (T/FAC or FEC), n = 1106, FAC or FEC, n = 230, FAC or FEC ± H and TH (TH/FAC or FEC ± H), n = 218, ET or AT, n = 74; T alone, n = 91.
significantly different between ILC and IDC (Supplementary Table 1).

Disease-free survival and overall survival were evaluated with a median follow-up time of 44 months (range, 1–221 months). In all, 290 patients had developed a recurrence (222 distant recurrences only, 19 local recurrences only, 49 distant and local recurrences), and 262 had died. Histological type was not associated with significant difference in overall survival (hazard ratio = 1.01; 95% CI, 0.7–1.47; \( P = 0.9 \)) (Figure 1) or local recurrence-free survival (hazard ratio = 0.8; 95% CI, 0.36–1.90; \( P = 0.65 \)) (Supplementary Figure 3).

DISCUSSION

We examined if patients with pure ILC benefit differently from neoadjuvant chemotherapy than patients with IDC. Approximately, 30–40% of IDCs are ER-negative and these cancers have different chemotherapy sensitivity and clinical behaviour compared with ER-positive IDCs (Arpino et al, 2004; Rouzier et al, 2005). Previous studies tried to adjust for the variable distribution of ER status by performing multivariate analysis. However, multivariate analysis has limitations particularly when confounders are only partially independent (Katz, 2003). In this study, we excluded ER-negative IDCs from the current analysis to address directly whether histology confers significant differences in sensitivity to neoadjuvant chemotherapy. Chemotherapy sensitivity was measured by pathological tumour response rates and the rate of breast-conserving surgery.

Similar to previous reports, we observed low pCR rates in both histological subtypes, IDC (14%) and ILC (3.5%) (Cocquyt et al, 2003; Mathieu et al, 2004; Cristofanilli et al, 2005; Tubiana-Hulin et al, 2006; Katz et al, 2007; Sullivan and Apple, 2009; Huober et al, 2010; Straver et al, 2010). However, pCR rates were not significantly different by histological type after adjusting for differences in tumour grade. This is different from earlier reports that suggested significantly lower pCR rates in ILC. Our results show that low- and intermediate-grade ILC and IDC both have similar, very low pCR rates. This result supports the idea that response to neoadjuvant chemotherapy in terms of pCR is more related to intrinsic tumour characteristics, reflected to some extent in grade than histology itself (Lips et al, 2012). Pathological complete response is a powerful early surrogate of good survival in ER-negative and HER2-positive cancers, but its prognostic value is less important in ER-positive cancers because many patients with

### Table 2. Surgical and pathological outcomes

| Final surgical outcome | ILC (n = 177) | IDC (n = 1718) |
|------------------------|--------------|---------------|
| No. of patients (%)    | %            | %             |
| Conservative           | 33 (19)      | 576 (34)      |
| Mastectomy             | 139 (79)     | 1078 (63)     |
| No surgery             | 5 (3)        | 64 (4)        |

| Pathological response  | ILC (n = 177) | IDC (n = 1718) |
|------------------------|--------------|---------------|
| No pCR                 | 165 (93)     | 1404 (82)     |
| pCR                    | 6 (3)        | 246 (14)      |

Abbreviations: IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; pCR = pathological complete response.

### Table 3. Predictors of mastectomy after neoadjuvant chemotherapy

| Factor         | Univariate analysis | Multivariate analysis |
|----------------|---------------------|-----------------------|
|                | OR* 95% CI P-value  | OR* 95% CI P-value    |
| Age (years)    | 0.99 0.98–1.00 0.02 | 0.99 0.98–1.00 0.02   |
| Multifocal tumour | —       | —        |
| No             | 1.00 —        | 1.00 —      |
| Yes            | 4.6 3.28–6.46 | 3.85 2.70–5.48 |
| Tumour size (cm) | 1.42 1.33–1.51 | 1.30 1.21–1.40 |

| N stage        | Univariate analysis | Multivariate analysis |
|----------------|---------------------|-----------------------|
| N0             | 1.00 —        | 1.00 —      |
| N1 or sup      | 2.03 1.66–2.48 | 1.39 1.09–1.77 |

| AJCC stage     | Univariate analysis | Multivariate analysis |
|----------------|---------------------|-----------------------|
| I/II           | 1.00 —        | 1.00 —      |
| III/IV         | 3.51 2.78–4.41 | 1.89 1.41–2.54 |

| Nuclear grade  | Univariate analysis | Multivariate analysis |
|----------------|---------------------|-----------------------|
| I              | 1.00 —        | 1.00 —      |
| II             | 0.81 0.47–1.37 | 1.43 0.75–2.69 |
| III            | 0.51 0.35–1.00 | 0.85 0.44–1.62 |

| Histological subtype | Univariate analysis | Multivariate analysis |
|----------------------|---------------------|-----------------------|
| IDC                  | 1.00 —        | 1.00 —      |
| ILC                  | 2.25 1.52–3.33 | 1.86 1.15–2.99 |

Abbreviations: AJCC = American Joint Committee on Cancer; CI = confidence interval; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; OR = odds ratio. OR = 1 is the reference; OR < 1, factor associated with lower mastectomy rate; OR > 1, factor associated with higher mastectomy rate.
extensive residual cancer continue to do well probably because of the benefit from adjuvant endocrine therapy (von Minckwitz et al, 2012). Our findings confirm that survivals were similar for both ER-positive IDC and ILC. We recognise that a median follow-up of 44 months is short for ER-positive breast cancers, which is a limitation of the current analysis. However, it is unlikely that late recurrence rates would differ significantly by histology among ER-positive cancers.

An important clinical benefit from neoadjuvant chemotherapy is clinical tumour response that leads to downstaging and smaller surgical resection volume (Fisher et al, 1998; Boughey et al, 2006).

| Table 4. Predictors of pathological complete response |
|---------------------------------|---------|-------------|-------------|---------|-------------|-------------|
| Factor                          | OR\(^a\) | 95% CI      | P-value     | OR\(^a\) | 95% CI      | P-value     |
| Age (years)                     | 0.99    | 0.98–1      | 0.2         | 1       | 0.99–1.01   | 0.8         |
| Multifocal tumour\(^b\)        |         |             |             |         |             |             |
| No                              | 1.00    | —           | —           | 1.00    | —           | —           |
| Yes                             | 0.69    | 0.48–1      | 0.05        | 0.75    | 0.5–1.12    | 0.15        |
| Nuclear grade                   |         |             |             |         |             |             |
| I                               | 1.00    | —           | —           | 1.00    | —           | —           |
| II                              | 4.91    | 0.67–36.14  | 0.1         | 2.91    | 0.38–22.56  | 0.31        |
| III                             | 20.33   | 2.81–147.17 | 0.002       | 11.26   | 1.47–86.39  | 0.01        |
| Baseline T stage                |         |             |             |         |             |             |
| T1–T2                           | 1.00    | —           | —           | 1.00    | —           | —           |
| T3–T4                           | 0.69    | 0.51–0.93   | 0.01        | 0.65    | 0.46–0.92   | 0.01        |
| Baseline N stage                |         |             |             |         |             |             |
| N0                              | 1.00    | —           | —           | 1.00    | —           | —           |
| N1 or sup                       | 0.73    | 0.56–0.96   | 0.02        | 0.66    | 0.49–0.9   | 0.008       |
| Histological subtype            |         |             |             |         |             |             |
| IDC                             | 1.00    | —           | —           | 1.00    | —           | —           |
| ILC                             | 0.21    | 0.09–0.47   | <0.001      | 0.5     | 0.19–1.3   | 0.1         |
| Neoadjuvant chemotherapy regimen|         |             |             |         |             |             |
| Taxane based\(^b\)              | 2.67    | 1.56–4.59   | <0.001      | 2.14    | 1.2–3.84   | 0.01        |
| Trastuzumab\(^c\)               | 6       | 4.44–8.12   | <0.001      | 5.03    | 3.64–6.95  | <0.001      |

Abbreviations: CI = confidence interval; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; OR = odds ratio; pCR = pathological complete response.
\(^a\)OR = 1 is the reference; OR < 1, factor associated with lower pCR rate; OR > 1, factor associated with higher pCR rate.
\(^b\)Taxane-based regimen was compared with no taxane-based regimen.
\(^c\)Trastuzumab regimen was compared with no trastuzumab regimen.

Figure 1. (A) Overall survival probability and (B) disease-free survival probability by histological subtype.
(≤ 2 mm) in ILC (19 vs 11%) and the rate of breast-conserving surgery was also lower (19 vs 34%). These differences in clinical benefit remained significant after adjusting for other clinical variables, including grade and tumour size. These observations are consistent with the majority of the literature that reports low rates of breast conservation therapy for patients with ILC following neoadjuvant chemotherapy (Soucy et al, 2008; Boughey et al, 2009). These results collectively indicate that clinical benefit from neoadjuvant chemotherapy in operable ER-positive ILC is less compared with ER-positive IDCs due to the inherently lower chemotherapy sensitivity of these cancers and their unique anatomical features, which make determination of cancer margins more difficult intraoperatively.

Our study is the largest report of outcomes of ILC subtype after neoadjuvant chemotherapy, but there were some limitations. As a retrospective survey there was heterogeneity in our population, especially regarding chemotherapy regimens. Moreover, important variables, such as proliferation (i.e. Ki-67 staining), were not available. However, nuclear grade may be considered as a crude surrogate for proliferation activity.

However, a simple conclusion that ILC does not respond to neoadjuvant chemotherapy would represent an oversimplification. Forty-one per cent of ILCs had lower tumour T stage compared with baseline after neoadjuvant chemotherapy. What further complicates clinical decision-making for patients with ILC is that clinical response rates over 50% have also been reported with the use of 3–6 months of neoadjuvant endocrine therapy alone (Eiermann et al, 2001; Cataliotti et al, 2006; Semiglavoz et al, 2007; Milneritsch et al, 2008; Mustacchi et al, 2009; Ellis et al, 2011). In addition, the majority of patients with ILC have a low or intermediate recurrence score (Oncotype DX, Redwood, CA, USA), which is associated with no or very modest benefit from adjuvant chemotherapy in terms of improved survival (Kelly et al, 2010; Mook et al, 2010; Allison et al, 2012). Taking all this information together, it is reasonable to conclude that most patients with ILC are unlikely to derive substantial short-term clinical benefit (substantial tumour reduction with clear margins or pathological CR) from neoadjuvant chemotherapy. However, ILC may derive similar long-term survival benefit from neoadjuvant chemotherapy as ER-positive IDCs, but this benefit is likely to be modest.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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