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The poor responsiveness of infiltrating lobular breast carcinomas to neoadjuvant chemotherapy can be explained by their biological profile

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Abstract

The aim of this study was to determine the chemosensitivity of infiltrating lobular breast carcinoma (ILC) in comparison with infiltrating ductal carcinoma (IDC). Between 1987 and 1995, 457 patients with invasive T2 > 3 cm–T4 breast carcinomas were treated with primary chemotherapy (CT), surgery, radiation therapy. Clinical response, the possibility of breast preservation, pathological response and survival were evaluated according to the histological type. In order to evaluate the biological differences between ILC and IDC patients and their implication with regard to tumour chemosensitivity, additional immunohistochemical stainings (oestrogen receptor (ER), Bcl2, p53, c-erbB-2 and Ki67) were performed on 129 pretherapeutical specimens. 38 (8.3%) ILC were diagnosed by core needle biopsy before CT. ILC was an independent predictor of a poor clinical response ($P = 0.02$) and ineligibility for breast-conserving surgery after neoadjuvant chemotherapy ($P = 0.03$). Histological and biological factors predicting a poor response to CT (histological grade, ER, Ki67 and p53 status) were more frequent in ILC than in IDC patients. After a median follow-up of 98 months (range: 3–166), the low chemosensitivity of ILC did not result in a survival disadvantage. Our results demonstrate that ILC achieved a lower response to CT than IDC because of their immunohistochemical profile. Pre-operative CT did not allow a high rate of conservative treatment for ILC and therefore the use of neoadjuvant CT for ILC patients should be questioned.

Keywords: Breast cancer; Infiltrating lobular carcinoma; Chemosensitivity; Infiltrating ductal carcinoma; Oestrogen receptor; Progesterone receptor; Neoadjuvant chemotherapy

1. Introduction

Infiltrating lobular carcinoma (ILC) of the breast is a subtype of carcinoma that accounts for 5–15% of cases. Differences in behaviour have been described between ILC and infiltrating ductal carcinomas (IDC). ILC are often more difficult to palpate and to visualise, both clinically and mammographically, than IDC. The prognosis of ILC has been described as either better or not different from that of IDC [1–3]. On the other hand, to our knowledge, chemosensitivity of ILC. Clinical response, pathological complete response (pCR) and pathological nodal status (pN) after neoadjuvant chemotherapy (CT) have been described as very strong indicators of survival, justifying their use as surrogate markers of chemosensitivity [4–6]. However, response to neoadjuvant CT according to the histological type of carcinoma has never been investigated.

The aim of this study was to evaluate the chemosensitivity of ILC by retrospectively investigating the response of ILC patients to neoadjuvant CT and to compare these findings with those observed in IDC patients. Biological markers (proliferative indexes,

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hormonal receptor status, histological grade, p53 status...) have been reported to be potential predictors of response to neoadjuvant CT [7–10]. Therefore, the biological characteristics of the ILC and IDC subtypes and their implication with regard to chemosensitivity were investigated using an immunohistochemical assay testing oestrogen receptor (ER), Bcl-2, p53, c-erbB-2 expression and Ki67 status.

2. Patients and methods

Our series comprised 457 consecutive patients treated at the Institute Gustave-Roussy between January 1987 and October 1995 for an operable, non-inflammatory, unilateral breast carcinoma exceeding 3 cm in diameter (T2-4, N0-2, M0) with preoperative chemotherapy followed by surgery. The mean age was 50 years (range 24–73 years). The diagnosis was established by a core needle biopsy. Before chemotherapy, two core needle biopsies (Tru-cut) of the breast tumour were performed: one for the histological analysis and one to determine the status of the ER and progesterone (PR) receptors. The histological type and the histoprognostic grade were analysed before treatment by two independent pathologists. The histological type was defined according to the World Health Organization (WHO) classification [11]. The histoprognostic grade was defined according to the modified Scarff, Bloom and Richardson (SBR) system described by Contesso and colleagues [12]. The steroid hormone receptor status was determined using the EIA (enzymo immunoassay) with ER-EIA and PR-EIA kits (Abbott Diagnostics). Tumours were considered positive when the ER or PR levels exceeded 10 fmol/mg of protein. In order to evaluate the biological differences between ILC and IDC and their implication with regard to tumour chemosensitivity, we performed additional immunohistochemical stainings on pretherapeutical specimens from between 1990 and 1995 when enough material was available from the core needle biopsies. ER status was validated by immunohistochemistry with the antibody 6F11 (Novocastra, Newcastle Upon Tyne, UK), dilution 1:30. Bcl2 and p53 expression and the c-erbB-2 status were evaluated with the 124 (Dakopatts) dilution 1:150, DO7 (Novocastra), dilution 1:250 and A485 (Dakopatts), dilution 1:700 antibodies, respectively. The proliferation rate was assessed by measuring Ki67 status with the MIB-1 antibody (Immunotech), dilution 1:50. Immunohistochemical stainings were performed in accordance with standard procedures on 4-μm sections of paraffin-embedded tissues. An antigen retrieval system was performed by heating slides in the microwave in citrate buffer. Two staining methods were applied: the peroxidase Envision system (Dako, France) for the monoclonal antibodies (ER, bcl2, p53, Ki67); and the peroxidase antiperoxidase method (PAP, Dako, France) for the polyclonal antibodies (c-erbB2). The scoring systems were as follows: nuclear staining $>10\%$ were scored positive for ER and p53 status; the Herceptest scoring method was used for the determination of c-erbB-2 status (0, 1+: negative; 2+, 3+: positive); bcl-2 status was scored positive if at least 10% of the tumour cells exhibited a cytoplasmic staining; a percentage of cells with nuclear staining with Ki67 monoclonal antibody $>20\%$ (median) was considered as the cut-off point to separate high proliferative tumours from low ones.

Preoperative CT consisted of three or four cycles of treatment: AVCMF (doxorubicin 50 mg/m^2, vincristine 1 mg/m^2, cyclophosphamide 600 mg/m^2, methotrexate 30 mg/m^2 and 5-fluorouracil 900 mg/m^2, intravenously (i.v.) on day 1) in 229 cases (50%) or FAC/FEC 50 (doxorubicin/epirubicin 50 mg/m^2, cyclophosphamide 600 mg/m^2 and 5-fluorouracil 900 mg/m^2) in 169 cases (37%) or FEC 100 (epirubicin 100 mg/m^2, cyclophosphamide 1000 mg/m^2 and 5-fluorouracil 1000 mg/m^2) in 59 cases (13%). Subsequent surgery was a lumpectomy when the tumour was less than 3 cm in diameter or a mastectomy for tumours exceeding 3 cm and bifocal tumours. Axillary dissection was performed in all cases. In 18 cases, a mastectomy was performed during a second operative procedure, either because the primary surgery was incomplete or because the margins of the operative specimen were involved after the lumpectomy.

Breast tissue without residual malignant epithelial cells, tumours with residual invasive malignant epithelial cells without mitosis and representing less than 5% of the tumour mass were classified in the group of pathological complete response (pCR). Tumours with a strictly *in situ* malignant residual component were also classified as pCR [13]. The number of histologically-positive axillary lymph nodes was determined through serial macroscopic sections of each lymph node.

Postoperative treatment consisted of two or three cycles of 5-fluorouracil (500 mg/m^2), doxorubicin (50 mg/m^2) and cyclophosphamide (500 mg/m^2) for patients treated with preoperative AVCMF or FAC 50. Patients treated with neoadjuvant FEC 50 or 100 regimen received two or three adjuvant courses of the same regimen. Locoregional radiotherapy was performed 2 weeks after the end of CT: 45 Gy were delivered to the internal mammary chain, supraclavicular nodes, chest wall or breast and a 15-Gy boost to the tumour margins when a lumpectomy was performed. Hormonotherapy with tamoxifen was given to menopausal patients and to premenopausal patients with a positive hormone receptor status.

The associations of variables were evaluated with the Chi-square test or with the Fisher's exact test where necessary. For non-categorical variables, the Mann–Whitney U test was used. The efficiency of neoadjuvant chemotherapy was assessed by evaluation of clinical response, possibility to perform a breast conservative

treatment and assessment of the pathological complete response. Age, histological type, initial clinical size and nodal status, histological grade, initial ER and PR status and CT regimen were tested in a univariate analysis. A logistic regression model was also performed to analyse independent factors associated with these markers of chemosensitivity. The starting date for survival analyses was the date of the initial tumour biopsy. Overall survival and disease-free survival (DFS) rates were estimated using the Kaplan–Meier method. Survival curves were compared for each parameter with the log rank test. A multivariate survival analysis using the Cox model was used to select independent factors. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software.

3. Results

In our series of 457 patients, 38 (8.3%) ILC were diagnosed by a core needle biopsy before CT: 34 specimens of the classic form, three of the alveolar variant and one of the pleomorphic variant. The 419 tumours that were not ILC were grouped into a subcategory of predominantly IDC tumours composed of 404 IDC, two mucinous carcinomas, one mixed IDC/ILC and 12 unspecified invasive carcinomas.

3.1. Clinical and pathological characteristics of ILC and IDC before treatment

Clinical and pathological characteristics according to histological subtype are reported in Table 1. ILC and IDC were not significantly different according to the patient's age, menopausal status, clinical tumour size, clinical nodal status and rate of bifocality. No ILC were grade III according to the SBR classification, while 37% of the IDC were ($P<0.001$). ILC were more frequently positive for the ER than IDC ($P=0.008$) (Table 1). There was no significant difference between IDC and ILC patients according to the type and dose of CT received.

3.2. Clinical response to neoadjuvant chemotherapy

The mean tumour size was 52 mm (SD: 14 mm) before neoadjuvant chemotherapy and 32 mm (SD: 17 mm) after. In the univariate analysis (Table 2), the histological type, initial tumour size, histological grade, PR status and CT regimen were significantly associated with the clinical response to chemotherapy. Clinical response to CT was lower for ILC compared with IDC: patients with ILC and IDC achieved 26% of complete or partial response to CT whereas patients with IDC achieved 58% of good clinical response; no complete clinical response was observed for ILC ($P=0.001$). In the multivariate analysis, the histological type, SBR grade and CT regimen were independent factors associated with a complete/partial clinical response to neoadjuvant chemotherapy (Table 3).

3.3. Eligibility for breast-conserving surgery after neoadjuvant chemotherapy

Initially, 214 patients underwent a breast-conserving surgery, but as 18 of these patients with positive margins underwent a mastectomy, 196 (43%) patients were treated with breast-conserving surgery, while 261 (57%) underwent a mastectomy. 16 patients with positive margins underwent an additional lumpectomy and 15 patients refused additional surgery. The proportion of tumours with a macroscopic tumour size exceeding 3 cm after CT was higher among ILC (55%) than IDC (32%) ($P=0.002$) and therefore the rate of conservative surgical

Table 1
Clinicopathological and biological characteristics of ILC and IDC before treatment

Characteristic	*n*	ILC 38 cases (*n*) (%)	IDC 419 cases (*n*) (%)	*P* value
Mean age (S.D.) (in years)	457	53 (9)	50 (10)	NS[a]
Menopausal status				
Premenopausal	248	22 (58)	226 (54)	
Postmenopausal	209	16 (42)	193 (46)	NS[b]
TNM classification: T				
T2	272	21 (55)	251 (60)	
T3	141	13 (34)	128 (31)	
T4	44	4 (11)	40 (9)	NS[b]
TNM classification: N				
N0	187	18 (47)	169 (40)	
N1	260	20 (53)	240 (57)	
N2	10	0	10 (2)	NS[b]
Bifocality				
No	446	38 (100)	408 (97)	
Yes	11	0	11 (3)	NS[b]
SBR[c] grade				
I	23	1 (3)	22 (6)	
II	250	32 (97)	218 (57)	
III	141	0	141 (37)	<0.001[b,d]
Missing	43	5	38	
Oestrogen receptor status[b]				
Positive	263	29 (91)	234 (68)	
Negative	112	3 (9)	109 (32)	0.008[b]
Missing	82	6	76	
Progesterone receptor status				
Positive	270	24 (71)	212 (61)	
Negative	89	10 (29)	136 (39)	NS[b]
Missing	98	4	71	

S.D., standard deviation; NS, non-significant; ILC, Infiltrating lobular carcinoma; IDC, Infiltrating ductal carcinoma.
[a] Student *t*-test.
[b] Chi-square test.
[c] Scarff Bloom and Richardson.
[d] SBR I and II versus III.

Table 2
Clinical response, surgical treatment and pathological response of ILC and IDC after neoadjuvant CT–univariate analysis (Chi-square test)

	Clinical response				Surgical treatment			Pathological response		
	Complete	Partial	Stable/ progression	*P* value	Lumpectomy	Mastectomy	*P* value	pCR[a]	Other	*P* value
Age (years)										
<50	20	109	97		102	124		29	197	
⩾50	16	107	108	0.61	94	137	0.34	15	216	**0.02**
Histological type										
Ductal	36	206	177		189	230		44	375	
Lobular	0	10	28	**0.001**	7	31	**0.001**	0	38	**0.04**
Initial size										
T2	29	124	119		149	123		33	239	
T3	7	66	68		40	101		10	131	
T4	0	26	18	**0.045**	7	37	**<0.001**	1	43	0.06
Initial nodal status										
N0	12	94	81		84	103		18	169	
N1	22	117	121		108	152		24	236	
N2	2	5	3	0.42	4	6	0.76	2	8	0.53
Histological grade										
SBR I	0	12	11		12	11		0	23	
II	15	108	127		93	157		14	236	
III	18	78	45	**0.002**	78	65	**0.004**	25	116	**<0.001**
Initial ER[b] status										
Positive	18	123	122		100	163		10	253	
Negative	8	61	43	0.35	55	57	**0.046**	21	91	**<0.001**
Initial PR[c] status										
Positive	12	108	116		87	149		10	226	
Negative	14	79	53	**0.025**	71	75	**0.023**	21	125	**<0.001**
Chemotherapy (CT) regimen[d]										
AVCMF	21	113	95		102	127		24	205	
FAC 560	3	13	11		10	17		0	27	
FEC 50	6	54	82		56	86		10	132	
FEC 100	6	36	17	**0.006**	28	31	0.609	10	49	**0.050**

[a] Pathological complete response
[b] Oestrogen receptor.
[c] Progesterone receptor.
[d] AVCMF,doxorubicin, vincristine, cyclophosphamide, methotrexate, 5-fluorouracil; FAC,5-fluorouracil, doxorubicin, cyclophosphamide; FEC,5-fluorouracil, epirubicin, cyclophosphamide.
Significant *P* values are in bold.

treatment was lower for ILC (18%) than for IDC (45%) ($P=0.001$) (Table 2). Lobular histology and initial tumour size were independent predictors of breast-conserving surgery ineligibility after neoadjuvant chemotherapy (Table 3).

3.4. Pathological response

Microscopic examination of the specimens revealed a complete pathological response in 44 cases (no infiltrating or *in situ* carcinoma in 31 cases and only microscopic foci of infiltrating carcinoma without mitosis in 13 cases). None of the 38 patients with ILC diagnosed before CT had a complete histological response after CT (Table 2). Factors associated with a complete pathological response in the univariate analysis were age, histological type, histological grade, ER status, PR status and CT regimen. In the multivariate analysis, initial tumour size and ER status were independent predictors of a complete pathological response. Certain margins considered negative at the examination of the frozen sections turned out to be positive at the definitive histological analysis: the rate of positive microscopic margins after lumpectomy was higher for ILC (9 of 12 cases, 75%) compared with IDC (40 of 202 cases, 20%) ($P<0.0001$). No difference was observed between ILC (63%) and IDC (65%) in the rate of axillary lymph node involvement after CT.

3.5. Immunohistochemical staining

In order to determine why the lobular histological subtype was associated with a poor response to chemotherapy, we conducted immunohistochemistry assays.

Table 3
Clinical response, surgical treatment and pathological response of ILC and IDC after neoadjuvant CT–multivariate analysis (logistic regression)

	Complete/partial clinical responses		Breast-conserving surgery		Complete pathological response	
	RR (95% CI)	*P* values	RR (95% CI)	*P* value	RR (95% CI)	*P* value
Age						
<50	1		1		1	
$\geqslant 50$	0.75 (0.47–10.19)	0.22	0.83 (0.51–10.33)	0.43	0.67 (0.29–10.6)	0.37
Histological type						
Ductal	1		1	1	1	
Lobular	0.36 (0.15–0.87)	**0.02**	0.24 (0.08–0.76)	**0.03**	0.003 (0.00–>10)	0.75
Initial size						
T2	1		1		1	
T3/4	0.90 (0.57–10.45)	0.68	0.22 (0.14–0.37)	$<$**0.001**	0.28 (0.11–0.76)	**0.01**
Initial nodal status						
N0	1		1		1	
N1/2	0.90 (0.56–10.45)	0.66	10.01 (0.61–10.66)	0.97	10.13 (0.46–20.75)	0.76
Histological grade						
SBR I/II	1		1		1	
III	10.94 (10.15–30.3)	**0.01**	10.45 (0.86–20.46)	0.17	10.9 (0.80–40.95)	0.14
Initial ER status						
Negative	1		1		1	
Positive	10.27 (0.71–20.27)	0.43	0.65 (0.36–10.19)	0.16	0.24 (0.09–0.63)	**0.004**
Initial PR status						
Negative	1		1		1	
Positive	0.73 (0.43–10.3)	0.27	0.87 (0.49–10.53)	0.62	0.49 (0.18–10.33)	0.16
CT regimen						
AVCMF	1		1		1	
FAC/FEC 50	0.63 (0.43–0.89)	**0.01**	10.04 (0.73–10.51)	0.80	0.97 (0.30–30.21)	0.97
FEC 100	10.69 (10.01–20.86)	**0.046**	0.87 (0.53–10.43)	0.58	0.50 (0.13–10.93)	0.32

RR, response rate; 95% CI, 95% Confidence Interval. Significant *P* values are in bold.

Before 1990, pretherapeutical specimens had been fixed in Bouin's solution compromising the results of the immunohistochemistry: these patients were not included in the immunohistochemistry assay. After 1990, enough prechemotherapy material was available for 129 cases. Results of the immunohistochemical assays are reported in Table 4. The immunohistochemically-determined ER status was statistically different between ILC and IDC patients ($P=0.02$). p53 status, c-erbB-2 expression and mean Ki67 were also statistically different between ILC and IDC samples ($P<0.001$, $P=0.012$ and $P=0.01$, respectively). The differences in the Bcl2 expression levels fell just short of statistical significance ($P=0.05$). These data clearly demonstrated that the biological profiles of ILC and IDC are different.

In this sub-set of 129 patients, the histological type of tumour was, as in the complete series of patients, significantly associated with a good or complete clinical response to chemotherapy: 57% of IDC (63/110) versus 21% of ILC (4/19) ($P=0.01$). None of the patients with ILC experienced pCR, but the difference with the IDC patients (10/110) was not significant probably due to a lack of power ($P=0.36$).

Clinical and pathological responses to neoadjuvant chemotherapy, according to histological and immunohistochemical data, are reported in Table 5. Histological grade ($P=0.03$), p53 status ($P=0.048$) and the Ki67 rate ($P=0.008$) were statistically associated with the clinical response. ER status ($P=0.05$), histological grade ($P=0.034$) and Ki67 rate ($P=0.01$) were significantly associated with the pCR. p53 status failed to reach statistical significance. Histological and biological factors predicting a poor response to CT were more frequent in the ILC tumours. Tumour differentiation (histological grade, ER status) and proliferation (Ki67) appeared to be the main factors explaining the low responsiveness of ILC to chemotherapy (Table 5).

3.6. Survival

The median follow-up was 98 months (range: 3–166 months). During the follow-up period, 50 local recurrences, 185 metastases and 162 deaths occurred. The disease-free survival (DFS) and overall survival rates were 52% (95% Confidence Intervals (CI): 46–58) and 57% (95% CI: 51–63), respectively. In the univariate

Table 4
Expression of biological markers in ILC and IDC

Markers		Infiltrating lobular carcinoma ($n=19$)	Infiltrating ductal carcinoma ($n=110$)	P value
ER-positive	n (%)	16 (84)	62 (56)	0.02[a]
p53-positive	n (%)	1 (5)	52 (47)	<0.001[a]
Bcl2-positive	n (%)	17 (89)	74 (67)	0.05[a]
c-erbB-2 positive	n (%)	1 (5)	37 (34)	0.012[a]
Ki67 rate	mean (±SEM)	14% (±4)	27% (±2)	0.01[b]
SBR III		0 (0)	45 (41)	0.001[a]

SEM, standard error of the mean.
[a] Chi-square test.
[b] Student t-test.

Table 5
Clinical and pathological response according to the immunohistochemical profile

		Clinical response		Pathological response		
	n	Mean rank	P value[a]	pCR	Other	P value[b]
Histological grade						
SBR I/II	81	58		3	78	
III	45	73	**0.03**	7	38	**0.034**
ER status						
Positive	78	71		3	75	
Negative	51	61	0.13	7	44	**0.05**
p53 status						
Positive	53	73		7	46	
Negative	76	60	**0.048**	3	73	0.09
Bcl2 status						
Positive	91	62		6	85	
Negative	38	71	0.22	4	34	0.48
c-erbB-2 status						
Positive	38	67		2	36	
Negative	91	64	0.77	8	83	0.72
Ki67 rate						
Low	50	51		0	50	
High	71	68	**0.008**	9	62	**0.01**

[a] Mann–Whitney U test
[b] Chi-square test.
Significant P values are in bold.

analysis, age < 50 ($P=0.03$), initial tumour size ($P=0.001$), initial nodal status ($P<0.001$), clinical response to neoadjuvant chemotherapy ($P<0.001$), surgical treatment ($P=0.001$), pathological response ($P=0.03$) and pathological nodal status ($P<0.001$) were associated with DFS (Table 6). In the multivariate analysis, the independent factors associated with poor DFS were age < 50 years ($P=0.03$), negative ER status ($P=0.009$), partial clinical response ($P=0.047$) and metastatic pathological nodal status ($P<0.001$). The 10-year overall survival rate was 74% (95% CI: 55–89) for ILC and 55% (95% CI: 49–61) for IDC. ILC did not emerge as a prognostic factor, either in the overall survival analysis nor in the DFS analysis (Table 6).

4. Discussion

The concept of delivering chemotherapy as primary treatment in early breast cancer patients is attractive because the chemosensitivity of the tumour can be assessed *in vivo* allowing for a more 'tailored' approach [14]. The results of our study indicate that ILC respond poorly to preoperative CT. A complete or partial

Table 6
Univariate (Log Rank) and multivariate (Cox's regression model) 10-year disease-free survival (DFS) analyses

	Univariate analysis					Multivariate analysis	
	5-year DFS (%)	SEM (%)	10-year DFS (%)	SEM (%)	*P* value	OR (95% CI)	*P* value
Age (years)	66	2.3	52	2.9			
<50	62	3.3	48	4.0		1	
$\geqslant 50$	71	3.1	56	4.1	**0.03**	0.68 (0.48–0.97)	**0.03**
Initial size							
T2	72	2.8	60	3.5		1	
T3	56	4.3	38	5.3		1.10 (0.84–1.43)	0.48
T4	64	7.5	45	9.0	**0.001**	1.10 (0.77–1.57)	0.61
Initial nodal status							
N0	77	3.2	63	4.6		1	
N1	59	3.2	44	3.7		0.94 (0.64–1.38)	0.74
N2	34	19	34	19	$<$**0.001**	1.65 (0.83–3.30)	0.16
Histological type							
Ductal	65	2.4	51	2.9		1	
Lobular	84	6.0	58	11	0.08	0.49 (0.21–1.15)	0.10
Histological grade							
SBR I	83	7.9	69	11		1	
II	68	3.0	49	4.1		1.20 (0.84–1.70)	0.33
III	62	4.3	57	4.6	0.34	1.24 (0.84–1.82)	0.28
Initial ER status							
Positive	71	2.9	54	3.9		1	
Negative	55	4.9	51	5.3	0.06	1.80 (1.16–2.79)	**0.009**
Initial PR status							
Positive	69	3.1	51	4.0		1	
Negative	60	4.2	53	4.9	0.44	1.14 (0.74–1.78)	0.53
CT regimen							
AVCMF	66	3.2	51	3.7		1	
FAC 50	53	9.9	53	9.9		1.45 (0.83–2.53)	0.19
FEC 50	65	4.1	50	5.3		1.07 (0.75–1.53)	0.72
FEC 100	78	5.8	75	6.0	0.19	0.63 (0.37–1.09)	0.10
Clinical response							
Complete	83	6.5	75	7.7		1	
Partial	74	3.1	59	4.2		1.50 (1.01–2.23)	**0.047**
Stable/progression	56	3.6	40	4.3	$<$**0.001**	1.93 (0.73–5.10)	0.18
Surgical treatment							
Lumpectomy	73	3.3	64	3.8		1	
Mastectomy	62	3.1	42	4.1	**0.001**	1.22 (0.79–1.9)	0.37
Pathological response							
pCR	79	6.3	74	7.4		1	
Other	65	2.3	50	3.0	**0.03**	1.08 (0.77–1.51)	0.87
Pathological nodal status							
pN0	84	3.0	77	3.9		1	
pN1	57	3.0	39	3.6	$<$**0.001**	2.73 (0.70–4.41)	$<$**0.001**

SEM, standard error of the mean; 95% CI, 95% Confidence Interval. Significant *P* values are in bold.

response to CT was obtained in 58% of IDC, but in only 26% of ILC ($P=0.001$). No complete clinical or pathological responses were observed for ILC patients. This low rate of clinical responses led to a poor rate of breast conservation therapy for the ILC patients treated with neoadjuvant chemotherapy. In contrast, the low response to chemotherapy did not result in a survival disadvantage. However, the biological study of the ILC patients in our series suggests that this type of breast carcinoma exhibits a pattern of characteristics that may explain both its low chemosensitivity and low aggressiveness.

The difference in behaviour between the ILC and IDC types has already been reported for early breast cancer patients. In most studies the prognosis of patients with ILC is better than that of those with IDC, whereas other

authors did not find any differences in terms of the overall survival rates [1–3]. It is possible that differences in the adjuvant therapies used might explain the differing results. Our results involved 457 women who had been treated in a single institution and followed-up for a median of 98 months (range: 3–166). Although our study is limited by its retrospective nature and the variety of chemotherapy regimens used, this important series allows us to draw some conclusions with regard to the chemosensitivity of the different breast cancer subtypes. This type of study should also allow a more tailored approach for patients with large breast tumours to be defined. In previously published series of large tumours treated with preoperative CT, the percentage of ILC (when specified) was between 7 and 12% [15,16]. Therefore, the actual number of ILC cases diagnosed was generally small as these reported series included less than 200 patients. In another series [4], the preoperative diagnosis of breast cancer was made using fine-needle aspiration. However, the sensitivity of this method to correctly subclassify lobular carcinoma is only 20% [17]. In our series, all pretreatment diagnoses were made by histological examination of core needle biopsies, thus allowing us to perform immunohistochemistry.

The rate of conservative treatment was lower for ILC patients (18%) compared with IDC (45%). This point is particularly crucial because breast-conserving surgery is the only demonstrated benefit resulting from neoadjuvant chemotherapy [4,18,19]. The macroscopic size of ILC after CT was large, this being partly linked to their diffuse and multicentric growth pattern. 9 of the 12 patients with ILC deemed eligible for breast-conserving surgery after neoadjuvant chemotherapy had undergone an additional surgical procedure (five mastectomies and four re-excisions). In our study, the second independent factor of a low response to CT was the type of CT regimen. The FAC/FEC 50 regimen was associated with a lower response rate. This is in accordance with the dose response relationship initially described for the epirubicin in patients with metastatic disease [20] and has recently been confirmed for neoadjuvant CT by Petit [21]. Two randomised phase III trials have demonstrated significant improvements in the clinical and pathological response rates following the sequential addition of docetaxel to an anthracycline-containing preoperative regimen: one of these trials was conducted in the Aberdeen Breast Centre [22] and the other was the NSABP B27 trial [23]. It will be of particular interest to investigate the response rate according to the histological type in these studies to determine if sequential taxanes are able to counteract the low response rate of ILC to anthracycline-based regimens.

In the multivariate analysis, the pathological response to neoadjuvant CT (Table 3) is related to the initial tumour size and ER status. Histological type did not reach statistical significance as no patients with ILC achieved a complete pathological response, resulting in a very broad confidence interval. Neoadjuvant CT has little impact on the outcome of patients with slowly-growing, sometimes neglected, large breast tumours with low proliferative indexes (low histological grade, positive ER status, low Ki67 index…). The clinical response, breast conservation and pathological complete response rates are low, while survival is quite good (Tables 3, 5 and 6). It may be hypothesized that neoadjuvant CT is inappropriate for these patients and that our results concerning ILC are because this histological type displayed, at least most of the time, the characteristics listed above (Tables 1 and 4). In fact, this study is limited by its retrospective nature, but it would be very interesting to stratify survival in randomised trials comparing adjuvant versus neo-adjuvant chemotherapy according to the histological type and the proliferative index.

The low response rate of ILC to CT could be related to their particular biological profile. The hormone receptor status and the proliferation rate have both been linked to response rates to CT in previous series [16,24]. Since 91% of ILC in our study exhibited a positive ER status and 100% had a SBR grade I or II, one could argue that the poor response rate of ILC may be due to its phenotype. However, the histological type remained an independent factor associated with a low clinical response in the multivariate analysis, while the hormone receptor status did not. The immunohistochemical results in our study may help to explain the chemoresistance of ILC. When compared with IDC, ILC had higher hormone receptor levels and bcl-2 expression and a lower Ki67 score and c-erbB-2 expression, as has been observed by others [1,3,25–28]. The relationship between mitotic activity and chemosensitivity has been extensively reported. In our study, it was the most significant factor associated with a clinical and pathological response. Interestingly, tumours that were highly proliferative have been demonstrated to exhibit a major response to cytotoxic agents, but also have high local and distant relapse rates [29,30]. A parallel can be drawn with the behaviour of ILC that did not respond to neoadjuvant chemotherapy but nevertheless have quite a favourable outcome. A tumour with a positive p53 status displayed a better clinical response to chemotherapy ($P = 0.048$) and was of border significance for a pathological response ($P = 0.09$). As only one ILC tumour exhibited a positive staining for p53, we can hypothesise that the p35 status could be one explanation for its poor chemosensitivity, even if the relationship between p53 and chemosensitivity is still debated in the literature. Some authors [31] have reported that overexpression of p53 is associated with chemosensitivity, whereas other found no such correlation [16,32] or have reported that p53-overexpressing tumours were chemoresistant [33–35]. In fact, there is a lack of

concordance between the methods used to determine the p53 status [36]. For lobular carcinomas, positive immunostainings have been reported to be rare and there has been little evidence of frequent mutations in the literature [27,37,38]. We cannot, from our study, determine the p53 status (wild-type or mutated) of the tumours according to their histological type because no frozen tissue had been preserved. Therefore, further studies are necessary to explore the relationship between p53 status and ILC to determine the role of p53 (if any) in the low chemosensitivity of ILC.

Other translational approaches, such as genomics or proteomics, will probably raise unanswered questions about chemosensitivity in the future and neoadjuvant chemotherapy will probably remain the therapy of choice. It is interesting to note that preliminary results obtained in small series demonstrated that microarray analyses could separate patients into four groups according to their expression of proliferation, c-erbB-2, ER and apoptosis genes [39]. Nevertheless, the study of thousands of genes using these methods will undoubtedly lead to a better understanding of the chemoresistance mechanisms in breast cancer patients.

The prognosis of ILC patients treated with preoperative CT has not been studied previously. In our present study, the overall survival rate of ILC and IDC patients was similar in the univariate analysis, although the response to CT was lower for the ILC patients. Independent factors for a better overall survival included a small tumour size, the absence of axillary node involvement after CT, the positivity of hormone receptors at diagnosis, and a complete or partial clinical response to CT. There are several reasons why the lack of chemosensitivity of ILC did not result in a survival disadvantage for these patients. Firstly, we cannot exclude a type II statistical error, as ILC represents only 8.3% of the patients included in this large series. Secondly, in some studies the natural course of ILC has been reported to be more favourable than that of IDC [2,3]. Thirdly, the almost systematic prescription of adjuvant tamoxifen may have counterbalanced the inefficiency of neoadjuvant chemotherapy because of an increased hormonosensitivity in the ILC patients.

5. Conclusions

The present study demonstrates that ILC achieved a lower response to CT than IDC. We also showed that the immunohistochemical profile of ILC can explain their low chemosensitivity. Preoperative CT did not allow a high rate of conservative treatment for ILC patients, unlike that achieved for the IDC patients and, therefore, the use of neoadjuvant CT for ILC patients should be questioned.

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