

Invasive ductal carcinoma and invasive lobular carcinoma of breast differ in response following neoadjuvant therapy with epidoxorubicin and docetaxel + G-CSF

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Received: 28 August 2006 / Accepted: 1 September 2006 / Published online: 24 October 2006
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Abstract

Purpose Preoperative chemotherapy in patients with primary breast cancer treated with anthracyclines and taxanes results in high response rates, allowing breast conserving surgery (BCS) in patients primarily not suitable for this procedure. Pathological responses are important prognostic parameters for progression free and overall survival. We questioned the impact of histologic type invasive ductal carcinoma (IDC) versus invasive lobular carcinoma (ILC) on response to primary chemotherapy.

Patients and Methods 161 patients with breast cancer received preoperative chemotherapy consisted of epidoxorubicin 75 mg/m² and docetaxel 75 mg/m² administered in combination with granulocyte-colony stimulating factor (G-CSF) on days 3–10 (ED + G). Pathological complete response (pCR), biological markers and type of surgery as well as progression free

and overall survival were compared between IDC and ILC.

Results Out of 161 patients, 124 patients presented with IDC and 37 with ILC. Patients with ILC were less likely to have a pCR (3% vs. 20%, $P < 0.009$) and breast conserving surgeries (51% vs. 79%, $P < 0.001$). Patients with ILC tended to have oestrogen receptor positive tumors (86% vs. 52%, $P < 0.0001$), HER 2 negative tumors (69% vs. 84%), and lower nuclear grade (nuclear grade 3, 16% vs. 46%, $P < 0.001$). Patients with ILC tended to have longer time to progression (TTP) (42 months vs. 26 months) and overall survival (69 months vs. 65 months).

Conclusions Our results indicate that patients with ILC achieved a lower pCR rate and ineligibility for BCS to preoperative chemotherapy, but this did not result in a survival disadvantage. Because of these results new strategies to achieve a pCR are warranted.

Keywords Docetaxel · Epidoxorubicin · Invasive ductal · Invasive lobular · Primary breast cancer

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Introduction

Preoperative cytotoxic chemotherapy is the standard treatment for patients presented with locally advanced breast cancer, and its use is extending to earlier stages of disease. This early use of chemotherapy can potentially avoid resistance and can possibly kill or inhibit clinically undetectable micrometastases to prevent or delay the development of metastatic disease. Pathologic complete response (pCR) and pathological nodal status after primary chemotherapy are considered surrogates for survival [1]. Another advantage in

applying chemotherapy preoperatively is the possibility of significant reduction in tumor size and therefore the improvement of both the rate and the cosmetic result of a breast conserving surgery (BCS) [1].

To date, anthracyclines and taxanes are the most active drugs in the treatment of advanced breast cancer, and a combination of these are considered to produce the highest response rates in the neoadjuvant as well as in the palliative treatment setting [2, 3].

However, primary chemotherapy has been extensively studied in breast cancer, but usually ductal and lobular carcinoma are considered together. No difference has been made concerning response, biologic markers and the ability of BCS between the two histological subtypes. Invasive lobular carcinoma (ILC) is the second most common type of invasive breast cancer after invasive ductal carcinoma (IDC), and accounts for 5–15% of all breast cancer cases [4]. Differences in behavior have been described between ILC and 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 [5, 6].

As a consequence of these data, we have initiated this prospective clinical evaluation to determine the impact of histologic type invasive lobular carcinoma versus invasive ductal carcinoma on response to primary cytotoxic chemotherapy with epirubicin and docetaxel plus granulocyte colony-stimulating factor in patients with breast cancer.

Patients and methods

Patients

One hundred and sixty one consecutive patients with histological proven breast cancer were accrued to this prospective evaluation between October 1999 and March 2005. All patients received a preoperative combination therapy consisting of epirubicin and docetaxel plus a granulocyte-colony stimulating factor (G-CSF).

Criteria for inclusion were as follows. Histologic proof of invasive breast cancer, age 18–70 years, Karnofsky performance status >80%, absence of distant disease, adequate hematologic parameters (white blood cell count $\geq 3,500/\mu\text{l}$, hemoglobin level >9 g/dl, and platelet count $\geq 100,000/\mu\text{l}$ (nl: 150–350 G/l), adequate hepatic (serum bilirubin < 1.5 mg/dl, transaminases < twice the upper limit of normal), and renal (serum creatinine < 1.5 mg/dl) function.

Drug administration

Treatment was administered on an outpatient setting. Preoperative chemotherapy consisted of 30-min intravenous short infusion epirubicin (Farmorubicin; Pfizer, New York, NY, USA) 75 mg/m^2 body surface area (BSA) followed by a 1-h infusion of docetaxel (Taxotere; Aventis, Strasbourg, France) 75 mg/m^2 BSA administered sequentially on day 1, accompanied by subcutaneous application of G-CSF (Neupogen; Amgen, Thousand Oaks, CA, USA) 30 MioIU from days 3–10, repeated every 21 days. Concomitant medication consisted of dexamethasone to prevent peripheral fluid retention and anaphylactic reactions [7], and ondansetron as prophylactic antiemetic therapy.

Treatment assessment

Baseline evaluations included a complete medical history, physical examination, complete blood count with differential, platelet count, and blood chemistry. Pathological diagnosis of invasive breast cancer, hormone-receptor status and HER2-status was performed in all patients by core-biopsy prior to their preoperative treatment. The histologic type was defined according to the World Health Organization classification [4]. Tumors which showed either mixed histologic types or types other than ductal or classic lobular were excluded to allow comparison of the pure lobular and ductal types. All patients were defined as hormone-receptor positive if either oestrogen receptor or progesterone receptor have turned out to be positive and as negative if both receptors were judged negative. HER2-receptor was judged positive if either HER2 has turned out to be immunohistochemistry (HercepTest[®], Dako A/S, Glostrup, Denmark) +++ positive or dual colour fluorescent in situ hybridization (FISH, PathVision[®] HER2 DNA probe kit, Vysis Inc., Downers Grove, IL, USA) positive, in case of a ++ positive IHC. P53-status was assessed by immunohistochemistry (ChemMate[®], Dako A/S, Glostrup, Denmark). The scoring system was as follows: nuclear staining >10% were scored positive for p53-status. Hormone-receptor- HER2-, and p53-status were assessed from the final surgical specimen after preoperative therapy. Due to possible cardiotoxic effects of this anthracycline-containing regimen, patients were required to have a normal baseline electrocardiogram and produce an echocardiography (left ventricular ejection fraction [LVEF] > 50%) prior to chemotherapy. The LVEF was monitored twice during treatment (begin and end of treatment). In order to exclude metastatic locations a computed tomography of the chest and abdomen and a bone-scan were required.

X-ray studies of selected osseous segments were performed when clinically indicated. Tumor size was determined by mammography, sonography, or magnetic resonance imaging (MRI). The most suitable radiological method was chosen to monitor the tumor site. According to the protocol, the neoadjuvant treated patients had to receive at least 2 cycles until a maximum of 8 cycles of the ED + G regimen until best possible response was achieved and were restaged every 2 cycles with mammography, sonography, or MRI. Based on these assessments, either a quadrantectomy with axillary node dissection (QUAD) or a modified radical mastectomy (MRM) was performed, depending on the size of the primary tumor after preoperative chemotherapy. Postoperative treatment consisted of the appropriate number of ED + G cycles in patients who received <6 cycles preoperatively in order to reach 6 cycles. Thereafter, treatment was adjusted according to the stage of the disease. Patients, who achieved a pCR received 4 cycles of the CMF regimen (cyclophosphamide 600 mg/m², methotrexate 40 mg/m² and 5-fluorouracil 600 mg/m²), all other patients were treated with 6 cycles of the CMF regimen. All patients, who experienced a BCS received postoperatively local irradiation and in case of positive hormone receptor status patients additionally tamoxifen 20 mg/day orally for a period of 5 years.

Therapy response was evaluated using the following criteria: Complete response (CR) was defined as the disappearance of all measurable disease in the breast and axillary nodes. Partial response (PR) was a $\geq 50\%$ decrease in tumor size. Stable disease (SD) was <50% decrease and <25% increase without the appearance of new lesions, and progressive disease (PD) was a more than 25% increase in tumor size or the appearance of new lesions. A pCR was defined as the absence of invasive tumor in the final surgical specimen after completion of the neoadjuvant therapy.

Statistical methods

The associations of variables were evaluated with the Chi-square-test. All statistics were calculated using the Statistical Package for the Social Sciences (SPSS[®] 12.0) software (SPSS[®] Inc. Headquarters, 233 S. Wacker drive, 11th floor, Chicago, Illinois 60606, USA). The distribution of TTP and OS were estimated using the Kaplan–Meier product-limit method.

Results

The pretreatment characteristics of the patients at diagnosis are summarized in Table 1. Out of 161

consecutive patients, 124 patients (77%) presented with IDC and 37 (23%) with ILC. The median patient age was 51 years (range 32–79 years) and 74 patients were premenopausal, 87 postmenopausal. The median follow up time was 68 months. All breast tumors were considered too large for upfront BCS. Table 2 shows the results of all pretreatment biological markers. Lobular carcinomas were more frequently hormone receptor positive (89% vs. 53%) and oestrogen receptor positive (86% vs. 52%, $P < 0.0001$) than ductal carcinomas and tended to be HER 2 negative (84% vs. 69%) and p53 negative (57% vs. 39%) than ductal carcinomas. ILC were more likely low-nuclear-grade disease (nuclear grade 3, 16% vs. 46%; $P < 0.001$) than IDC.

In the neoadjuvant treatment all patients were evaluable for pathological response (Table 3). Cytostatic treatment was stopped in 141 patients (88%) because best possible clinical response was achieved and in the other 20 patients (12%) because of SD. Pathologically, a major response (pCR + PR) was observed in 133 of 161 patients (83%), with 26 patients (16%) experiencing a pCR of the invasive tumor and 107 patients (66%) showing a PR. Analyzing the patients by histology a major response in 25 patients (68%) with ILC and in 108 patients (87%) with IDC, could be demonstrated, respectively ($P < 0.005$). A pCR could be reached in one patients (3%) with ILC and in 25 patients (20%) with IDC ($P < 0.009$). Twenty-four patients (65%) with ILC and 83 patients (67%) with IDC reached a PR. ILC tended to have a higher incidence of a residual lymph node disease than IDC (59% vs. 48%).

Breast conserving surgery (BCS) was possible in 117 (73%) patients and 44 (27%) patients underwent MRM, (Table 3). Patients with ILC were more likely than those with IDC to undergo MRM (49% vs. 21%). The proportion of patients who underwent BCS was significantly lower for patients with ILC (51%) than those with IDC (79%; $P < 0.001$). ILC was an independent predictor of ineligibility for BCT:

At a median follow-up time of 68 months (range: 6–111 months), 52 patients (32%) had developed a recurrence and 29 patients (18%) had died. Eighteen patients (11%) were lost to follow-up, 6 patients with ILC and 12 patients with IDC, respectively. Eight patients (22%) with ILC and 44 patients (35%) with IDC developed a recurrence. Time to progression (TTP) was median 42 months (range: 11–71 months) in patients with ILC and 26 months (range: 5–96 months) in patients with IDC, respectively. Four patients (10%) with ILC and 25 patients (18%) with IDC died. Overall survival (OS) was median 69 months

Table 1 Pretreatment patients characteristics

	Overall (<i>n</i> = 161)		IDC (<i>n</i> = 124)		ILC (<i>n</i> = 37)		<i>P</i> -value
	No. of Patients	%	No. of Patients	%	No. of Patients	%	
Age, years: [median (range)]		51 (32–79)		50 (32–73)		54 (38–79)	
Premenopausal	74	46	59	48	15	41	
Postmenopausal	87	54	65	52	22	59	
Preoperative tumor size							
T ₀ -T ₂	78	48	62	50	16	43	
T ₃ -T _x	83	52	62	50	21	57	
Lymph nodes preoperatively							
Negative	67	42	54	44	13	35	
Positive	94	58	70	56	24	65	n.s.
Nuclear grade							
1	12	7	9	7	3	8	
2	73	45	46	37	27	73	
3	63	39	57	46	6	16	0.001
ND	13	8	12	10	1	3	
Therapy cycles: [median (range)]	6 (3–10)		6 (3–10)		5 (3–6)		

Abbreviations: IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma

Table 2 Pretreatment biological markers

	Overall (<i>n</i> = 161)		IDC (<i>n</i> = 124)		ILC (<i>n</i> = 37)		<i>P</i> -value
	No. of Patients	%	No. of Patients	%	No. of Patients	%	
ER and PR							
Both negative	61	40	57	46	4	11	
Either positive	91	59	66	53	33	89	n.s.
ER positive	97	60	65	52	32	86	0.0001
ER negative	63	39	58	47	5	14	
PR positive	60	37	39	31	21	57	
PR negative	100	63	84	68	16	43	
ND	1	1	1	1	–	–	
HER 2 Status							
Negative	117	73	86	69	31	84	n.s.
Positive	38	24	34	27	4	11	
ND	6	3	4	4	2	5	
p53 Status							
Negative	69	43	48	39	21	57	n.s.
Positive	35	22	33	27	2	5	
ND	57	35	43	34	14	38	

Abbreviations: ER, oestrogen receptor; PR, progesterone receptor; ND, not done

Table 3 Pathological response

	Overall (<i>n</i> = 161)		IDC (<i>n</i> = 124)		ILC (<i>n</i> = 37)		<i>P</i> -value
	No. of Patients	%	No. of Patients	%	No. of Patients	%	
Pathological response							
pCR	26	16	25	20	1	3	0.009
PR	107	66	83	67	24	65	
OR = pCR + PR	133	82	108	87	25	68	0.005
SD	28	18	16	13	12	32	
PD	–	–	–	–	–	–	
Surgery							
BCS	117	73	98	79	19	51	0.001
MRM	44	27	26	21	18	49	

Abbreviations: pCR, pathological complete response; PR, partial response; OR, overall response; SD, stable disease; PD, progressive disease; BCS, breast conserving surgery; MRM, modified radical mastectomy

(range: 16–108 months) in patients with ILC and 65 months (range: 6–111 months) in patients with IDC, respectively. Reaching a pCR did not have a statistical significant influence on TTP and OS between patients with ILC and IDC. However, only one patient with ILC reached a pCR, therefore we could not well assess whether achievement of pCR was associated with a favorable outcome in this cohort of patients. Patients with invasive lobular disease tended to have better TTP (42 months vs. 26 months) and OS (69 months vs. 65 months) than patients with invasive ductal disease, indicating that TTP and OS were different between the two histologic types.

Discussion

Preoperative chemotherapy is increasingly used in the management of breast cancer. It is considered to be the standard of care for patients with locally advanced and inoperable breast tumors for inducing tumor shrinkage that may render inoperable tumors amenable to surgery. However, preoperative chemotherapy is also a possibility for patients with operable tumors leading to smaller breast resection and better cosmetic outcome. Moreover, preoperative chemotherapy permits in vivo assessment of tumor response and consequently provides an opportunity to predict outcome and tailor therapy [8]. Achieving a pCR of the invasive tumor is the most important aim of applying chemotherapy preoperatively because this is considered a powerful early surrogate of long-term survival [9].

Preoperative chemotherapy regimens, including anthracyclines and taxanes, are the most active cytotoxic schedules in the treatment of primary breast cancer and are considered to produce the highest overall response and pCR rates [2, 10]. Therefore, we decided to apply a combination regimen consisting of epidoxorubicin and docetaxel to all included patients in this prospective clinical evaluation.

Reviewing the literature, neoadjuvant chemotherapy has been extensively studied in patients with breast cancer, but usually ductal and lobular carcinoma are considered together. ILC represents only 5–15% of all breast cancer subtypes. In contrast with IDC, the tumor is characterized by ill-defined thickening and induration of the breast and can be difficult to recognize clinically and mammographically. This is related to the histological growth pattern of the tumor: diffusely infiltrating neoplastic cells around large amounts of fibrous tissue [11]. These clinical and pathological features make early diagnosis, adequate staging and

treatment evaluation of ILC before definitive surgery difficult [12].

To our knowledge, this is the first prospective clinical evaluation to determine the impact of histologic type invasive lobular carcinoma versus invasive ductal carcinoma which administered the same combination chemotherapy regimen, epidoxorubicin and docetaxel plus G-CSF, for all included patients with primary breast cancer. In our evaluation patients with ILC tended to hormone-receptor positive tumors (89% vs. 53%), especially oestrogen-receptor (ER) positive tumors (86% vs. 52%, $P < 0.0001$), HER two negative tumors (69% vs. 84%), and higher nuclear grade (nuclear grade 3, 16% vs. 46%, $P < 0.001$). Therefore only few patients with ILC achieve a pCR to primary chemotherapy ($P < 0.0098$) leading to ineligibility for BCS ($P < 0.001$) after preoperativ cytostatic treatment. It is well known that ER-positive tumors, low nuclear grade and huge tumor size are associated with minor response to preoperative chemotherapy [13, 14]. In our evaluation we could demonstrate that 25 patients (20%) with IDC achieved a pCR after receiving chemotherapy preoperatively. These tumors were HER2-positiv ($P < 0.005$) and showed a high nuclear grade. These two factors are well known for chemosensitivity.

The relationship between p53-status and chemosensitivity is still debated in the literature. Some authors [15] have reported that overexpression of p53 is associated with chemosensitivity, whereas other did not found such correlations [16], or have reported that p53-overexpressing tumors were chemoresistant [17]. In fact, there is a lack of concordance between the methods used to determine the p53-status [18, 19]. We cannot, from our study, exactly determine the p53-status (wild-type, mutated or deleted) of the tumors according to immunohistochemistry, because no gene sequencing was performed. On the other hand our patient population is also too small to evaluate the impact of reaching a pCR to primary chemotherapy depending of the p53-status.

Interestingly, after a median follow up of 58 months the low chemosensitivity of ILC did not result in a survival disadvantage. This is in accordance with a recently published retrospective study on 860 patients receiving different preoperative chemotherapy regimens [20]. Therefore primary chemotherapy in patients with ILC does not achieve the two main objectives for this treatment: adequate downstaging of disease to allow for BCS and provision of a surrogate marker of prognosis (pCR).

In conclusion, our study indicate that ILC was an independent predictor of a poor clinical response and ineligibility for BCS after preoperativ cytostatic

treatment. Histological and biological factors predicting a poor response to neoadjuvant chemotherapy (ER and low nuclear grade) were more frequent in ILC than in IDC patients. In contrast, the low response of ILC to preoperative chemotherapy did not result in a survival disadvantage. Because of these differences between ILC and IDC in patients receiving chemotherapy preoperatively, results of preoperative studies who did not stratified between ILC and IDC must be interpreted with care. In future histology must be used as a stratum in prospective randomized studies. Therefore the use of preoperative chemotherapy for patients with ILC may not be the best standard of care for these patients and should be questioned. New strategies for patients with ILC to achieve a pCR must be developed. Additional investigation, including genomic and proteomic studies, are warranted clarifying the unique biologic features of this disease.

References

1. Fisher B, Brown A, Mamounas, et al (1997) Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. *J Clin Oncol* 15:2483–2493
2. Wenzel C, Locker GJ, Schmidinger M, et al (2002) Combined analysis of two phase II trials in patients with primary and advanced breast cancer with epidoxorubicin and docetaxel + granulocyte colony stimulating factor. *Anticancer Drugs* 13:67–74
3. Sparano JA, O'Neill A, Schaefer PL, et al (2000) Phase II trial of doxorubicin and docetaxel plus granulocyte colony-stimulating factor in metastatic breast cancer. Eastern Cooperative Oncology Group Study E1196. *J Clin Oncol* 18:2369–2377
4. The World Health Organization (1982) The World Health Organization histological typing of breast tumors second edition. *Am J Clin Oncol* 78:806–816
5. Silverstein MJ, Lewinsky BS, Waisman JR, et al (1994) Infiltrating lobular carcinoma. Is it different from infiltrating duct carcinoma? *Cancer* 73:1673–1677
6. Toikkanen S, Pylkkanen L, Joensuu H (1997) Invasive lobular carcinoma of the breast has better short- and long-term survival than invasive ductal carcinoma. *Br J Cancer* 76:1234–1240
7. Dieras V, Chevallier B, Kerbrat P, et al (1996) A multicentre phase II study of docetaxel 75 mg/m² as first-line chemotherapy for patients with advanced breast cancer: report of the clinical screening group of the EORTC. *Br J Cancer* 74:650–656
8. Cristofanilli M, Gonzales-Angulo A, Sneige N, et al (2005) Invasive lobular carcinoma classic type: response to primary chemotherapy and survival outcomes. *J Clin Oncol* 23:41–48
9. Fisher B, Bryant J, Wolmark N, et al (1998) Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J Clin Oncol* 16:2672–2685
12. Von Minckwitz G, Raab G, Caputo A, et al (2005) Doxorubicin with cyclophosphamide followed by docetaxel every 21 days compared with doxorubicin and docetaxel every 14 days as preoperative treatment in operable breast cancer: The GEPARDUO study of the German Breast Group. *J Clin Oncol* 23:2676–2685
11. Silva O, Zurrida S (2000) Breast cancer: a practical guide. Breast pathology. Kidlington, Oxford, UK: Elsevier Science, pp 56–64
12. Cocquyt VF, Blondeel PN, Depypere HT, et al (2003) Different responses to preoperative chemotherapy for invasive lobular and invasive ductal breast carcinoma. *EJSO* 29:361–367
13. Bear HD, Anderson S, Brown A, et al (2003) The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from national surgical adjuvant breast and bowel project protocol B-27. *J Clin Oncol* 21:4165–4174
14. Guarneri V, Broglio K, Kau S-W, et al (2006) Prognostic value of pathologic complete response after primary chemotherapy in relation to hormone receptor status and other factor. *J Clin Oncol* 24:1037–1044
15. Bertheau P, Plassa F, Espie M, et al (2002) Effect of mutated TP53 on response of advanced breast cancers to high-dose chemotherapy. *Lancet* 360:852–854
16. Makris A, Powles TJ, Dowsett M, et al (1995) P53 protein overexpression and chemosensitivity in breast cancer. *Lancet* 345:1181–1182
17. Kandioler-Eckersberger D, Ludwig C, Rudas M, et al (2000) TP53 mutation and p53 overexpression for prediction of response to neoadjuvant treatment in breast cancer patients. *Clin Cancer Res* 6:50–56
18. Soong R, Robbins PD, Dix BR, et al (1996) Concordance between p53 protein overexpression and gene mutation in a large series of common human carcinomas. *Hum Pathol* 27:1050–1055
19. Mathieu M-C, Rouzier R, Llombart-Cussac A, et al (2004) The poor responsiveness of infiltrating lobular breast carcinomas to neoadjuvant chemotherapy can be explained by their histological profile. *Eur J Cancer* 40:342–351
20. Tubiana-Hulin M, Stevens D, Lasry S, et al (2006) Response to neoadjuvant chemotherapy in lobular and ductal breast carcinomas: a retrospective study on 860 patients from one institution. *Ann Oncol* 17:1228–1233