Effect of adjuvant chemotherapy in postmenopausal patients with invasive ductal versus lobular breast cancer

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Background: On the basis of the lack of response of invasive lobular breast cancer to neoadjuvant chemotherapy, we questioned the effectiveness of adjuvant chemotherapy in relation to histology.

Patients and methods: Women with primary nonmetastatic invasive ductal or (mixed type) lobular breast cancer, aged 50–70 years, diagnosed between 1995 and 2008, were selected from the Netherlands Cancer Registry and followed until January 1, 2010. The patients were divided in two groups: one group receiving adjuvant hormonal therapy only and the other receiving adjuvant hormonal therapy in combination with adjuvant chemotherapy.

Results: In total, 19,609 patients had ductal cancer and 3,685 had lobular cancer. The 10-year overall survival rate in ductal cancer when treated with hormonal therapy alone was 69%, compared with 74% with the combination therapy ($P < 0.0001$). In lobular cancer, 10-year survival rates were 68% after hormonal treatment alone and 66% after the combination therapy ($P = 0.45$). The hazard ratio (HR) for mortality in ductal cancer after combination therapy was 0.70 [95% confidence interval (CI) 0.64–0.76; $P < 0.0001$], compared with hormonal treatment alone. The HR in lobular cancer was 1.00 (95% CI 0.82–1.21; $P = 0.97$).

Conclusion: Adjuvant chemotherapy seems to confer no additional beneficial effects in postmenopausal patients with pure or mixed type lobular breast cancer receiving hormonal therapy.

Key words: adjuvant chemotherapy, histology, hormonal treatment, invasive ductal carcinoma, invasive lobular carcinoma, survival

Introduction

Invasive lobular carcinoma (ILC) is, next to invasive ductal carcinoma (IDC), the second most common type of breast cancer, with a reported incidence of 5%–15% of all breast cancer cases [1, 2]. Owing to its specific clinical, biological and prognostic features, classic (or pure) lobular carcinoma is often considered to represent a distinct clinical entity, different from IDC [3–5].

The introduction of neoadjuvant chemotherapy in the early 1980s has highlighted the relevance of distinguishing between lobular and ductal carcinoma in clinical decision making. Currently, neoadjuvant chemotherapy is the standard treatment for patients presenting with locally advanced breast cancer [6, 7]. However, owing to the practical benefit of downsizing the tumor, the use of neoadjuvant chemotherapy has extended to primary operable breast cancer to increase the rate of breast-conserving therapy [8, 9]. Another major advantage of neoadjuvant chemotherapy is that it offers the opportunity for an in vivo assessment of chemosensitivity of the tumor [10]. Recent studies have shown an inferior response of hormone receptor-positive ILC to neoadjuvant chemotherapy, compared with IDC [11–13]. This difference is most pronounced when looking at pathological complete response. Reported proportions of patients with a pathological complete response range from 0% to 3% for patients with ILC, compared with 6%–15% for those with IDC [14, 15]. Despite growing evidence of a poorer response of hormone receptor-positive, classical ILC to neoadjuvant chemotherapy, no prospective randomized study of the effectiveness of the adjuvant use of chemotherapy in these patients exists. Consequently, these patients might be exposed to ineffective treatment regimens with associated side-effects [14–16].
Previous research from our group based on a Dutch regional cohort of more than 2000 patients questioned this efficacy of adjuvant chemotherapy in patients with ILC [17]. Although a trend toward poorer efficacy was indeed observed in patients with ILC, the numbers were too small for a firm conclusion. Therefore, a nationwide analysis of data from the Netherlands Cancer Registry (NCR) was performed to evaluate the effect of adjuvant chemotherapy in addition to hormonal treatment in postmenopausal women with primary, nonmetastatic ILC, compared with those with IDC and mixed type ILC. We hypothesized that patients with ILC would benefit less from adjuvant chemotherapy compared with patients with IDC.

**methods**

**patient selection**

Patient data were derived from the population-based NCR covering data on all newly diagnosed in situ and invasive tumors. The NCR is deemed complete since 1989. Notification is mainly obtained from the automated pathology archive. Other sources are the National Registry of Hospital Discharge Diagnoses and radiotherapeutic departments. Specially trained registration clerks collect data on patient-, tumor- and treatment characteristics from patient hospital files. Owing to thorough registrar training, computerized consistency checks and regular national quality checks, the quality of the data is considered high [18].

All postmenopausal patients having invasive ductal, lobular or mixed type lobular breast cancer were selected. For this study, we defined postmenopausal patients as those aged between 50 and 70 years [19]. The patients were treated with adjuvant therapy according to the national treatment guidelines of that specific period [20]. In these guidelines, the decision for the use of chemotherapy was based on tumor size, nodal status and histologic tumor grade, and the use of hormonal therapy was restricted to patients with hormone receptor-positive breast cancer. Chemotherapy was not recommended for patients over 70 years of age. Histologic subtype has never been an indication for the use of adjuvant systemic therapy in the national guidelines.

In order to evaluate the additional effect of adjuvant chemotherapy, the patients were divided in two groups. One group received hormonal therapy only, while the second group received a combination of adjuvant hormonal and chemotherapy.

According to the NCR, 144,831 women were diagnosed with invasive breast cancer and underwent surgery in the Netherlands in the period 1995–2008, of whom 70,324 were between 50 and 70 years of age. From these 70,324 patients, we excluded 851 patients with metastatic disease at diagnosis of the primary tumor (stage IV disease). Of the remaining 69,473 patients, 65,314 had IDC, ILC or mixed type ILC. In total, 24,685 patients had received either adjuvant hormonal treatment alone or adjuvant hormonal treatment in combination with chemotherapy. This group constituted the study population. No distinction was made between the different types of hormonal treatment or chemotherapy.

Tumor types have been classified by the NCR according to the International Classification of Diseases for Oncology (ICD-O) [21]. ICD-O codes 8010, 8020, 8140, 8141, 8201, 8230, 8500, 8501, 8521, 8523 and 8541 were used to define IDC. ILC was defined by ICD-O code 8520 and mixed type ILC by code 8522.

**statistical analysis**

Differences in disease and treatment characteristics between patients with IDC, ILC and mixed type ILC were calculated using the chi-square test. Information on vital status was obtained from the nationwide municipal population registries network. These registries provide virtually complete coverage of all deceased Dutch citizens. The patients were followed until their reported date of death or until January 1, 2010. The time to death was estimated using the life-table method and was considered to be the interval between the date of primary treatment and the date of death. The overall survival rates were calculated according to the type of adjuvant systemic treatment (either hormonal treatment alone or hormonal treatment in combination with chemotherapy) and for each histologic type separately. The survival rates of subgroups were compared using the log rank-test.

A multivariate analysis was performed using a Cox proportional-hazards model to determine the impact of chemotherapy in addition to hormonal treatment, for each histologic tumor type separately. Separate multivariate analyses were also performed for patients receiving hormonal treatment or hormonal treatment in combination with chemotherapy to determine the prognostic effect of tumor histology. Finally, multivariate analyses were performed to test for interaction between histologic tumor type and use of chemotherapy in addition to hormonal treatment. In all multivariate analyses, we adjusted for age at diagnosis, postoperative tumor (pT) size, axillary nodal status (pN) and tumor grade.

**results**

**characteristics**

Between January 1995 and December 2008, a total of 24,685 women with invasive breast cancer had received hormonal treatment or hormonal treatment in combination with chemotherapy. This group consisted of 19,609 patients (79%) with IDC, 3685 patients (15%) with ILC and 1391 (6%) with mixed type ILC. The baseline characteristics of these three subgroups are summarized in Table 1.

Only small differences were observed in absolute size with respect to age at diagnosis, period of diagnosis and axillary nodal status. Larger absolute differences were observed with respect to tumor size and grade. Here, patients with ILC presented with larger tumors at the time of diagnosis, compared with patients with IDC, while fewer poorly differentiated (grade 3) tumors were observed among the patients with ILC, compared with those with IDC and mixed type ILC. In addition, information on tumor grade was missing for 35% of the patients with ILC, compared with 26% of those with mixed type ILC and 14% of those with IDC. The patients with ILC and mixed type ILC were less likely to undergo breast-conserving surgery and to receive locoregional radiotherapy, compared with those with IDC. The three groups of patients with IDC, ILC and mixed type ILC were fully comparable concerning the administration of hormonal and systemic treatment. Of all the patients, 58% were treated with hormonal therapy alone, while 42% received hormonal therapy combined with chemotherapy.

**overall survival**

The median follow-up time for the total patient group was 5.6 years. The 10-year survival for patients with IDC treated with hormonal therapy alone was 69.2%, compared with 74.5% for those treated with hormonal therapy and chemotherapy (Figure 1A), which was a statistically significant difference ($P < 0.0001$). For patients with ILC, the 10-year survival rate was 68.0% after hormonal treatment alone and 66.3% after hormonal therapy with chemotherapy (Figure 1B). This
difference was not statistically significant ($P = 0.45$). For patients with mixed type ILC, the 10-year survival was 73.2% after hormonal treatment alone and 68.1% after adjuvant hormonal therapy in combination with chemotherapy ($P = 0.33$) (Figure 1C).

**multivariate analyses**

The multivariate analysis according to the histologic subtype (Table 2) showed that the patients with IDC receiving adjuvant hormonal treatment with chemotherapy had a significantly lower mortality risk when compared with those receiving only hormonal treatment [hazard ratio (HR) 0.70, 95% confidence interval (CI) 0.64–0.76; $P < 0.0001$]. Among the patients with ILC or mixed type ILC, no effect of additional chemotherapy was observed on overall survival, with a HR of 1.00 (95% CI 0.82–1.21; $P = 0.965$) and 0.98 (95% CI 0.70–1.34; $P = 0.829$), respectively.

In a multivariate analysis of overall survival for the patients receiving hormonal treatment with chemotherapy, no significant differences were observed between the different histologic subtypes (Table 3). In a separate analysis for the patients who received hormonal treatment only, those with ILC had a significantly better survival than those with IDC (HR, 0.86; 95% CI 0.77–0.95; $P = 0.003$).

A statistically significant interaction was observed between the use of adjuvant chemotherapy and histologic tumor type (Table 1). In a model including patients with ILC and IDC, those with IDC were demonstrated to have a 29% lower mortality risk when receiving chemotherapy in addition to hormonal therapy (HR, 0.71; 95% CI 0.65–0.78), whereas no statistically significant reduction after chemotherapy was observed for patients with ILC (HR, 0.90; 95% CI 0.76–1.06). The $P$-value for interaction was 0.014. In a model including patients with mixed type ILC and IDC, the $P$-value for interaction between use of adjuvant chemotherapy and histologic type was 0.004.

Adding use of locoregional radiotherapy as a covariate to the aforementioned multivariate models did not substantially alter the estimated hazard ratios (HRs).

**Discussion**

The present study strongly suggests that patients with ILC and mixed type ILC do not seem to benefit from the addition of chemotherapy to hormonal treatment in the adjuvant setting. In contrast, patients with IDC do show a relative risk reduction in mortality of about 17% by this regimen, which might be expected on the basis of the results of the patient-level meta-analysis of randomized trials by the Early Breast Cancer Trialists’ Collaborative Group and the estimates provided by prognostic calculators and decision-making tools, such as ADJUVANT! [19, 22]. Thus, as estrogen and progesterone receptor status are important predictors of the response to hormonal treatment, this study indicates that the histologic subtype of the primary tumor also plays an important role in predicting the response to adjuvant chemotherapy in postmenopausal women with hormonal sensitive breast cancer.

This remarkable difference between ductal and lobular cancer in the response to adjuvant chemotherapy was demonstrated in a multivariate analysis, stratified according to histologic subtype, which resulted in completely nonoverlapping HRs for mortality of 0.70 (95% CI 0.64–0.76; $P < 0.0001$) for IDC and 1.00 (95% CI 0.82–1.21; $P = 0.965$) for ILC. The lack of effect of chemotherapy was also illustrated by a multivariate analysis stratified according to the use of adjuvant chemotherapy. Here, the patients with ILC showed a significantly lower mortality risk than those with IDC when receiving hormonal treatment alone (HR 0.86; 95% CI 0.77–0.95; $P = 0.03$), whereas among the patients receiving chemotherapy in addition to hormonal treatment, those with ILC tended to have a worse prognosis than those with IDC (HR 1.11; 95% CI 0.94–1.30; $P = 0.229$). These findings may illustrate either that lobular breast cancer patients do worse on...
Figure 1. (A) Overall survival for patients aged 50–70 years with invasive ductal breast cancer; hormonal treatment with chemotherapy versus hormonal treatment alone. (B) Overall survival for patients aged 50–70 years with invasive lobular breast cancer; hormonal treatment with chemotherapy versus hormonal treatment alone. (C) Overall survival for patients aged 50–70 years with invasive mixed type lobular breast cancer; hormonal treatment with chemotherapy versus hormonal treatment alone.
combination therapy—perhaps because of serious side-effects such as cardiomyopathy, myelodysplastic syndrome and leukemia—or that ductal breast cancer patients do significantly better. Anyhow, the role of histologic subtype in the prognosis of systemic treatment outcome is substantial. Finally, the role of histologic subtype as a modifier of the effect of chemotherapy was confirmed by including histology and chemotherapy as an interaction term in the multivariate model.

Our results provide further evidence that ILC should be seen as a different entity, apart from IDC, with a very good response to hormonal therapy alone. As has been suggested by others, the addition of chemotherapy in this group of patients might even worsen the prognosis [23]. It has been hypothesized that the lack of sensitivity of ILC to chemotherapy is explained by the inactivation of E-cadherin in ILC, which is thought to increase the transition of lobular carcinoma cells to mesenchymal cells, which in turn become more resistant to chemotherapy [24]. It has been demonstrated that lobular and ductal carcinomas of the breast have distinct genomic and expression profiles [25]. For example, mutations in exon 9 of the PIK3CA gene are more frequent in ILC than in IDC and these mutations are independently associated with early recurrence and death [26, 27]. In experimental breast cell line models, PIK3CA gene mutations increase kinase activity, promote cell growth and proliferation, are associated with

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**Table 2. Multivariate analysis of overall survival for patients with invasive breast cancer, aged 50–70 years, receiving hormonal treatment with or without chemotherapy, according to histologic subtype**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ductal (n = 18 185) Hazard ratio for events (95% CI)</th>
<th>P</th>
<th>Pure lobular (n = 3426) Hazard ratio for events (95% CI)</th>
<th>P</th>
<th>Lobular Mixed (n = 1296) Hazard ratio for events (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03 (1.02–1.03)</td>
<td>&lt;0.0001</td>
<td>1.04 (1.03–1.06)</td>
<td>&lt;0.0001</td>
<td>1.02 (1.00–1.05)</td>
<td>0.117</td>
</tr>
<tr>
<td>Nodal status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pN1mi versus pN0</td>
<td>1.04 (0.86–1.27)</td>
<td>0.686</td>
<td>1.27 (0.81–1.97)</td>
<td>0.297</td>
<td>0.80 (0.39–1.65)</td>
<td>0.548</td>
</tr>
<tr>
<td>pN1a versus pN0</td>
<td>2.10 (1.90–2.33)</td>
<td>&lt;0.0001</td>
<td>2.39 (1.86–3.07)</td>
<td>&lt;0.0001</td>
<td>1.62 (1.09–2.42)</td>
<td>0.018</td>
</tr>
<tr>
<td>pN &gt; 1a versus pN0</td>
<td>2.79 (2.44–3.20)</td>
<td>&lt;0.0001</td>
<td>3.39 (2.52–4.56)</td>
<td>&lt;0.0001</td>
<td>3.65 (2.27–5.87)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Tumor size</td>
<td>T2 versus T1</td>
<td>1.68 (1.56–1.81)</td>
<td>1.59 (1.32–1.92)</td>
<td>&lt;0.0001</td>
<td>1.31 (1.22–2.18)</td>
<td>0.001</td>
</tr>
<tr>
<td>T3-4 versus T1</td>
<td>2.88 (2.57–3.22)</td>
<td>&lt;0.0001</td>
<td>1.94 (1.55–2.43)</td>
<td>&lt;0.0001</td>
<td>3.18 (2.19–4.63)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Grade</td>
<td>2 versus 1</td>
<td>1.61 (1.36–1.91)</td>
<td>&lt;0.0001</td>
<td>1.14 (0.82–1.58)</td>
<td>0.433</td>
<td>1.61 (0.89–2.92)</td>
</tr>
<tr>
<td></td>
<td>3 versus 1</td>
<td>2.71 (2.30–3.20)</td>
<td>&lt;0.0001</td>
<td>1.54 (1.07–2.22)</td>
<td>0.021</td>
<td>2.37 (1.31–4.31)</td>
</tr>
<tr>
<td></td>
<td>x versus 1</td>
<td>2.38 (2.00–2.82)</td>
<td>&lt;0.0001</td>
<td>1.42 (1.04–1.95)</td>
<td>0.027</td>
<td>1.85 (1.03–3.32)</td>
</tr>
<tr>
<td>Systemic adjuvant treatment</td>
<td>Hormonal + chemotherapy versus hormonal alone</td>
<td>0.70 (0.64–0.76)</td>
<td>&lt;0.0001</td>
<td>1.00 (0.82–1.21)</td>
<td>0.965</td>
<td>0.98 (0.70–1.33)</td>
</tr>
</tbody>
</table>

**Table 3. Multivariate analysis of overall survival for patients with invasive breast cancer aged 50–70 years, according to the type of adjuvant systemic treatment**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hormonal treatment with chemotherapy (n = 9700) Hazard ratio for death (95% CI)</th>
<th>P</th>
<th>Hormonal treatment only (n = 13 207) Hazard ratio for death (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.05 (1.04–1.06)</td>
<td>&lt;0.0001</td>
<td>1.02 (1.02–1.03)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nodal status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pN1mi versus pN0</td>
<td>0.75 (0.50–1.13)</td>
<td>0.166</td>
<td>1.13 (0.94–1.37)</td>
<td>0.201</td>
</tr>
<tr>
<td>pN1a versus pN0</td>
<td>2.12 (1.71–2.63)</td>
<td>&lt;0.0001</td>
<td>2.11 (1.90–2.34)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>pN &gt; 1a versus pN0</td>
<td>2.92 (2.32–3.66)</td>
<td>&lt;0.0001</td>
<td>2.96 (2.54–3.44)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Tumor size</td>
<td>T2 versus T1</td>
<td>1.63 (1.42–1.87)</td>
<td>&lt;0.0001</td>
<td>1.69 (1.56–1.98)</td>
</tr>
<tr>
<td>T3-4 versus T1</td>
<td>2.73 (2.28–3.26)</td>
<td>&lt;0.0001</td>
<td>2.58 (2.29–2.91)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Grade</td>
<td>2 versus 1</td>
<td>1.48 (1.13–1.94)</td>
<td>0.005</td>
<td>1.53 (1.29–1.81)</td>
</tr>
<tr>
<td></td>
<td>3 versus 1</td>
<td>2.72 (2.09–3.56)</td>
<td>&lt;0.0001</td>
<td>2.40 (2.03–2.85)</td>
</tr>
<tr>
<td></td>
<td>x versus 1</td>
<td>2.07 (2.56–2.75)</td>
<td>&lt;0.0001</td>
<td>2.12 (1.79–2.52)</td>
</tr>
<tr>
<td>Histologic type</td>
<td>Lobular versus ductal</td>
<td>1.11 (0.94–1.30)</td>
<td>0.229</td>
<td>0.86 (0.77–0.95)</td>
</tr>
<tr>
<td></td>
<td>Lobular-mixed versus ductal</td>
<td>1.16 (0.89–1.50)</td>
<td>0.270</td>
<td>0.96 (0.80–1.15)</td>
</tr>
</tbody>
</table>
metastatic capability and confer increased resistance to paclitaxel [28].

Another observation in our study was that the patients with mixed type ILC tended to respond in a similar way to chemotherapy as the patients with pure ILC. This finding is in line with previous reports on the pathological and prognostic differences between IDC, pure ILC and mixed type ILC [29, 30]. However, this retrospective analysis is the first study that calls into question the efficacy of adjuvant chemotherapy when added to hormonal therapy for patients with ILC and mixed type ILC.

The conclusions of our study are valid for women between 50 and 70 years of age. Although not presented here, the same analyses were performed for the premenopausal—under 50 years of age—group. During the studied time period (1995–2008), the post- to premenopausal ratio was 2:1 in this cohort and of the premenopausal patients who had been treated with adjuvant systemic treatment, only 9% had received hormonal treatment alone. Although the trends in these premenopausal patients for each of the three histologic types appeared to be similar to those in the postmenopausal patients, subgroups became too small to draw conclusions [17].

Some limitations of our study have to be considered, which are inherent to the registry-based, nonrandomized design. In our nationwide cohort, covering a period of 14 years, patients have probably been receiving different types and durations of adjuvant hormonal treatment and different chemotherapeutic regimens, depending on the prevailing guideline. As the Dutch guidelines have never included histologic subtype as an indication for the use of adjuvant systemic treatment, we assume that this potential mix of systemic treatment regimens has not been a significant confounding factor in our analyses.

The same conclusion in fact holds for the meta-analyses by Early Breast Cancer Trialists’ Collaborative Group, in which randomized trials were included that date all the way back to the 1970s [19]. Another potential limitation was the relatively large number of patients with lack of information on tumor grade, especially for those with ILC. It is still controversial whether ILC actually should be graded in the same way as IDC, as no tubule formation occurs in ILC, which could explain why so many of these cancers had unknown grade and were mostly well (grade 1) or moderately (grade 2) differentiated [5]. Furthermore, no central pathology review was undertaken and no distinction could be made with our data between classic and pleomorphic ILC. Given the fact that pleomorphic ILC may display high proliferative rates, low expression of hormone receptors and even HER2 positivity [31], our overall findings might not apply to this specific lobular carcinoma subtype. Finally, it has to be noted that the median follow-up of 5.6 years is still relatively short for evaluating effects of adjuvant systemic treatment in breast cancer.

In the future, traditional prognostic factors, including nodal status, tumor size and histologic grade and type, will probably be replaced by gene expression profiles. Although a growing number of studies are initiated to validate the currently available gene profiles, such as the 70-gene MammaPrint signature and 21-gene Oncotype DX signature, more research is needed on how these profiles can be used to predict the response to chemotherapy in individual patients [32, 33].

To our knowledge, this large, population-based study is the first study focusing on the influence of histologic subtype on the effect of adjuvant systemic therapy and the first presenting evidence of the lack of effect of adjuvant chemotherapy in postmenopausal ILC and mixed type ILC patients. Our findings are of great clinical importance, both for the individual patient and for public health. In the United States, the absolute number of postmenopausal patients with newly diagnosed mixed or pure ILC is about 20,000 per year [14]. Omitting possible ineffective chemotherapy in a substantial part of these patients will significantly reduce morbidity and costs. Still, our results need to be confirmed by other studies. It is unlikely that a future randomized trial concerning this subject will be accomplished. Therefore, we advise to reanalyze the individual patient data of previously performed randomized controlled trials on adjuvant systemic treatment with long-term follow-up, taking into account histologic subtype. Furthermore, other large population-based databases can be evaluated. Also, further research on the type of chemotherapy administered to patients with lobular breast cancer should be carried out. Until now, it is not clear whether there is a difference in effectiveness between chemotherapy regimens. If confirmed by other studies, our results could be an important step forward in tailoring chemotherapy for patients with breast cancer.

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disclosure
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references


