Low-dose tamoxifen in the treatment of breast ductal intraepithelial neoplasia: results of a large observational study

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Background: Tamoxifen’s cost–benefit ratio for breast ductal intraepithelial neoplasia (DIN) is unclear. Since low-dose tamoxifen showed a favorable modulation of breast cancer biomarkers in phase II trials, a monocentric cohort of women with DIN treated with low-dose tamoxifen or no systemic treatment was analyzed.

Patients and methods: A total of 309 patients with DIN received low-dose tamoxifen as part of institutional guidelines and were compared with 371 patients with DIN who received no systemic treatment after surgery.

Results: Women with estrogen receptor (ER)/progesterone receptor (PgR) >50% DIN who were not treated had a higher incidence of breast events than women on tamoxifen [hazard ratio (HR) 1.76; 95% confidence interval (CI) 1.00–3.12] or women with ER/PgR <50% DIN [HR 1.72; 95% CI 1.14–2.58]. Among untreated patients with ER >50% DIN, recurrence was higher in PgR <50% DIN than in PgR >50% DIN, whereas it was similar among low PgR (<50%) DIN against which tamoxifen had no effect. No difference in endometrial cancer incidence was noted.

Conclusions: High ER and especially high PgR expression is a significant adverse prognostic indicator of DIN, and low-dose tamoxifen appears to be an active treatment. Women with low-expression ER or PgR DIN do not seem to benefit from tamoxifen. A definitive clinical trial is warranted.

Key words: breast cancer, DCIS, ductal intraepithelial neoplasia, low-dose tamoxifen

introduction

Tamoxifen’s benefit in the treatment and prevention of estrogen receptor (ER)-positive breast cancer is well established [1–3]. However, treatment-related side-effects, such as endometrial cancers and venous thromboembolic events, still pose a complex clinical decision making particularly in women with early or premalignant disease.

In its early clinical development, tamoxifen was administered at daily doses of 30 and 40 mg for the treatment of advanced breast cancer. In order to decrease toxicity, the dose was then empirically reduced to 20 mg/day, despite the lack of data from properly designed studies. Most findings in the adjuvant and prevention settings have been obtained with this dosage.

Over the last 10 years, our group has focused on the search for the optimal biological tamoxifen’s dose, i.e. the minimal active dose which may maintain benefits while minimizing its toxicity. Studies have shown that the 20 mg/day dose could be reduced to 5 or even 1 mg/day with retained antiproliferative effects on breast cancer [4]. As the endometrial effect of tamoxifen is dose dependent [5], lower doses were shown to favorably modulate breast cancer and cardiovascular risk biomarkers without increasing endometrial proliferation and menopausal symptoms [6].

The standard post-surgical treatment of ductal intraepithelial neoplasia (DIN) remains debated. Two large phase III clinical trials assessed the effect of tamoxifen 20 mg/day for the reduction of breast cancer recurrence in women with DIN with slightly different results [7, 8]. While the NSABP-B24 showed a lower breast cancer recurrence rate in women allocated to tamoxifen compared with placebo [7], no additional benefit of tamoxifen over radiotherapy was observed in the UK–Australian trial [8]. At our institution, the use of low-dose tamoxifen for the adjuvant treatment of DIN has been offered to women since early 2001. In a previous study [9], the administration of any medical treatment including a variety of hormonal and retinoid agents was shown to be associated with a borderline significant 45% lower risk of breast cancer events in women with ER-positive, HER-2-negative DIN. In the
present analysis, in order to provide additional clues on the best treatment of women with DIN, we assessed the effect of low-dose tamoxifen on breast cancer recurrence according to the expression level of ER and progesterone receptor (PgR).

patients and methods

patients’ characteristics

Women who underwent breast cancer surgery at the European Institute of Oncology from 1 January 1999 to 31 December 2005, diagnosed for DIN with ER-positive staining (21%) and followed up to 31 December 2008 were included in the study cohort. Routine measurement of ER and PgR on DIN began in January 1998. Routine measurement of HER2/neu overexpression began in December 1999. A dedicated database was developed in order to collect all relevant clinical data including demographics, personal history, surgical treatment, tumor histology, post-surgical treatment, clinical trial participation and follow-up data.

Women were considered postmenopausal if they had not experienced a menstrual period in the 6 months before diagnosis or if they were receiving hormone replacement therapy (HRT). Patients were excluded if they had a previous breast cancer including DIN, if they had undergone presurgical systemic treatment or if they had positive axillary lymph nodes.

treatment assignment

All treatments were assigned in compliance with the Helsinki Declaration. All clinical trials conducted in the cohort have been approved by the Ethics Committee of the European Institute of Oncology and all subjects have signed informed consent, when appropriate. From January 2001, all cases were discussed on a weekly basis by a multidisciplinary team to evaluate the most appropriate post-surgical treatment, including participation in clinical trials. Some differences in treatment selection over the 10-year follow-up period were observed due to the fact that no standard guidelines on post-surgical treatment of DIN had been drawn up and that the multidisciplinary team started working only in January 2001. For instance, radiotherapy was recommended to women with DIN, or DIN, disease [10] upon a combination of risk factors (such as young age, presence of comedo histology or necrosis and positive margin involvement) and was not administered to women with a DIN, disease. Similarly, low-dose tamoxifen treatment to ER-positive DIN patients changed during the observation period: outside clinical studies, no hormonal treatment was routinely recommended. However, given the promising results of several phase II trials conducted in our institution [4, 6, 11], from January 2004, low-dose tamoxifen treatment, be it 5 mg/day or 20 mg/week, was discussed directly with the patients, in case they were ER-positive DIN.

statistical methods

The primary end point was disease-free survival, calculated from the date of surgery to any local or regional recurrence, contralateral breast cancer, death from breast cancer or to the last visit date, whatever occurred first. For patients with multiple breast cancer episodes during follow-up, only the first episode was considered in the analysis. Other primaries and non-breast cancer-related deaths were considered as competing events. Crude cumulative incidence was computed in a competing risk framework as described by Marubini and Valsecchi [12] and compared across different subgroups by means of the Gray test. The multivariate Cox proportional hazards regression model was used to evaluate the effect of treatments adjusted for clinical and pathological prognostic features.

Percentages were compared using the chi-square test or the Fisher exact test, where appropriate. All analyses were carried out with the SAS software (SAS Institute, Cary, NC) and the R software package (available at www.r-project.org). All tests were two sided.

results

A total of 680 patients with a median age of 51 years (range 26–84 years) were included. Of these, 81 (12%) were aged 40 years or younger. Table 1 summarizes the main baseline characteristics of the entire cohort and of the two groups of patients according to whether they received tamoxifen or no systemic treatment. Overall, 341 (50%) women were premenopausal at the time of diagnosis and 21% of the cohort had a first- or second-degree family history of breast cancer. As regards histology, most DIN were solid or cribriform (79%), moderately or well differentiated (82%), with a low proliferating index (Ki-67 <20%, 72%) and with high ER-positive expression immunostaining (90% with ER ≥50%). HER-2/neu was overexpressed (3+) in ~22% of the DIN. Relatively to the control group, patients receiving low-dose tamoxifen were younger and more frequently received radiotherapy (Table 1).

The patient distribution according to ER and PgR expression is shown in Figure 1. While ER showed a skewed distribution toward high levels, with a median value of 90%, PgR had a uniform distribution, with a median value of 40%. Overall, 296 patients (44%) had highly positive ER and PgR values, both >50%.

A total of 309 (45%) patients with ER-positive disease received low-dose tamoxifen (either 5 mg/day or 20 mg/week, approximately half each) as part of a clinical trial or as an institutional guideline for risk reduction regardless of radiotherapy. The median drug exposure was 32 months (range 0.1–73 months). Conversely, 371 patients were not administered any systemic treatment because they preferred not to take any drug after surgery or received placebo in clinical trials or had medical contraindication to tamoxifen.

After a median follow-up of 66 months (range 11–132 months), a total of 124 events occurred, as shown in Table 2. The median time interval to the diagnosis of any local or locoregional recurrence was 33 months (range 8–49 months). No difference in terms of other primary cancer has been observed including endometrial cancers (1 versus 2, in tamoxifen versus no treatment group, respectively). Overall, the 5-year cumulative incidence of DIN-related event was 14.5% [95% confidence interval (CI) 11.9% to 17.5%, Figure 2A] with a statistically significant negative trend according to age. The 5-year cumulative incidence was 44.9%, 26.0%, 15.7% and 10.4% for class ranges <35, 35–40, 41–50 and >50 years, respectively (P < 0.001, Figure 2B).

There was no statistically significant difference between patients who received low-dose tamoxifen and those who did not as for cumulative incidence of breast events (13.2% versus 15.8%, respectively, P = 0.262, Figure 2C). However, patients with highly positive ER and PgR (>50%) DIN who did not receive tamoxifen had a significantly higher incidence of events compared with patients with a highly positive ER/PgR DIN who received tamoxifen [hazard ratio (HR) 1.76; 95% CI 1.00–2.58] in whom tamoxifen was ineffective. A similar trend was observed both in pre- and postmenopausal women, as well as in the subgroup of patients who underwent breast-conserving surgery, irrespective of radiotherapy (data
No difference was observed in the few patients who underwent mastectomy.

Furthermore, in the subset of HER-2/neu-negative DIN, patients with highly positive ER/PgR DIN who did not receive low-dose tamoxifen showed a higher incidence of events compared with the remaining patient groups (HR 1.61; 95% CI 1.02–2.53) and to patients with a highly positive ER/PgR DIN who received tamoxifen (HR 1.67; 95% CI 0.90–3.09). In the subset of HER-2/neu-positive disease, patients with a highly positive ER/PgR DIN who did not receive low-dose tamoxifen showed a higher incidence of events compared with the remaining patient groups (HR 1.61; 95% CI 1.02–2.53) and to patients with a highly positive ER/PgR DIN who received tamoxifen (HR 1.67; 95% CI 0.90–3.09).

Table 1. Baseline characteristics of the entire cohort and of patients’ subgroups according to treatment

<table>
<thead>
<tr>
<th></th>
<th>Total, n (%)</th>
<th>Low-dose tamoxifen, n (%)</th>
<th>No treatment, n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;35</td>
<td>17 (3)</td>
<td>1 (0.3)</td>
<td>16 (4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>35–40</td>
<td>64 (9)</td>
<td>35 (11)</td>
<td>29 (8)</td>
<td></td>
</tr>
<tr>
<td>41–50</td>
<td>253 (37)</td>
<td>137 (44)</td>
<td>116 (31)</td>
<td></td>
</tr>
<tr>
<td>51–65</td>
<td>261 (38)</td>
<td>109 (35)</td>
<td>152 (41)</td>
<td></td>
</tr>
<tr>
<td>&gt;65</td>
<td>85 (13)</td>
<td>27 (9)</td>
<td>58 (16)</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. (Continued)

<table>
<thead>
<tr>
<th></th>
<th>Total, n (%)</th>
<th>Low-dose tamoxifen, n (%)</th>
<th>No treatment, n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2/neu overexpression Present 140 (22) 58 (19) 82 (24) 0.14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent 501 (78) 243 (81) 258 (76)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery BCS 534 (79) 253 (82) 281 (76) 0.052</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mastectomy 146 (21) 56 (18) 90 (24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiotherapy BCS only None 338 (63) 148 (58) 190 (68) 0.007</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERIL1 26 (5) 14 (6) 12 (4)</td>
<td></td>
<td></td>
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</tbody>
</table>

Differences are tested by the chi-square test; numbers in bold face are statistically significant.

aComedo versus other.
bAny radiotherapy versus no radiotherapy.

ER, estrogen receptor; PgR, progesterone receptor; BCS, breast-conserving surgery; BC, breast cancer; ERIL1, electron beam intraoperative radiotherapy.

Figure 1. Distribution of estrogen receptor (ER) and progesterone receptor (PgR).

not shown). No difference was observed in the few patients who underwent mastectomy.

Furthermore, in the subset of HER-2/neu-negative DIN, patients with highly positive ER/PgR DIN who did not receive low-dose tamoxifen showed a higher incidence of events compared with the remaining patient groups (HR 1.61; 95% CI 1.02–2.53) and to patients with a highly positive ER/PgR DIN who received tamoxifen (HR 1.67; 95% CI 0.90–3.09). In the subset of HER-2/neu-positive disease, patients with a highly positive ER/PgR DIN who did not receive low-dose tamoxifen
showed a higher incidence of events compared with the remaining patient groups (HR 1.62; 95% CI 0.58–4.52) and with patients with a highly positive ER/PgR DIN who received tamoxifen (HR 2.18; 95% CI 0.35–13.6).

Finally, the prognostic significance of PgR was further investigated in the subgroup of patients with highly positive ER DIN (≥50%, Figure 3). The risk of recurrence in untreated subjects was higher in highly positive PgR DIN (≥50%) than in low PgR expression (<50%), whereas it was similar in women who had lower PgR expression (<50%), where tamoxifen was ineffective.

**discussion**

Thanks to the widespread use of mammographic screening, the incidence of DIN has rapidly increased in the last decade. DIN represents a wide spectrum of breast neoplasms with an excellent prognosis for which no general consensus on postsurgical treatment has been obtained [13–16].

Two phase III trials have assessed tamoxifen’s role (20 mg/day) in the reduction of both invasive and noninvasive neoplasms. Table 2 shows the total number of events and the number of events in the low-dose tamoxifen and no-treatment groups.

**Table 2. First neoplastic event or death from any cause**

<table>
<thead>
<tr>
<th>Event</th>
<th>Total, n (%)</th>
<th>Low-dose tamoxifen, n (%)</th>
<th>No treatment, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local <em>in situ</em></td>
<td>42 (6.2)</td>
<td>16 (5.2)</td>
<td>26 (7.0)</td>
</tr>
<tr>
<td>Contralateral <em>in situ</em></td>
<td>9 (1.3)</td>
<td>7 (1.9)</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Local invasive</td>
<td>32 (4.7)</td>
<td>11 (3.6)</td>
<td>21 (5.7)</td>
</tr>
<tr>
<td>Locoregional invasive</td>
<td>9 (1.3)</td>
<td>7 (2.3)</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Contralateral invasive</td>
<td>17 (2.5)</td>
<td>6 (1.9)</td>
<td>11 (3.0)</td>
</tr>
<tr>
<td>Other primary</td>
<td>9 (1.3)</td>
<td>2 (0.7)</td>
<td>7 (1.9)</td>
</tr>
<tr>
<td>Deaths from breast cancer</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Deaths from other causes</td>
<td>5 (0.7)</td>
<td>1 (0.3)</td>
<td>4 (1.1)</td>
</tr>
<tr>
<td>Total</td>
<td>124 (18.2)</td>
<td>50 (16.2)</td>
<td>74 (19.9)</td>
</tr>
</tbody>
</table>

*Low-dose tamoxifen: 1 endometrium, 1 rectum; No treatment: 2 endometrium, 1 ovary, 1 colon, 1 central nervous system, 1 lymphoma, 1 kidney.*

**Figure 2.** Cumulative incidence of first neoplastic event, including *in situ* and invasive breast neoplasm, invasive locoregional recurrence, *in situ* and invasive contralateral breast neoplasm and death from breast cancer. Panel (A): unstratified cumulative incidence; panel (B): cumulative incidence stratified by age; panel (C): cumulative incidence stratified by treatment; panel (D): Cumulative incidence stratified by treatment and hormone receptor status. CI, confidence interval; ER, estrogen receptor; PgR, progesterone receptor.
An important finding of our study is the significant adverse prognostic effect of ER and PgR expression level, with a higher 5-year cumulative incidence of first event in tumors expressing both ER and PgR >50% relative to tumors with either ER or PgR below that level. Despite a positive ER expression in invasive breast cancer has long been regarded as a favorable prognostic factor compared with ER poor tumors, some authors have argued that an opposite relationship might exist, especially in younger patients and after standardized immunohistochemistry methods [18–20]. Moreover, the prognosis of women with ER-positive and ER-negative tumors tends to converge after 5–6 years since diagnosis [21] and the St Gallen Consensus Panel has defined ER status only as a predictive and not as a prognostic factor [22]. Our findings derived from a large series of untreated cases indicate that women with high hormone receptor expression DIN have a higher recurrence risk compared with women with lower receptor expression, most probably as a result of a greater sensitivity to endogenous hormone effect. In line with this notion, our results show that a high PgR expression is the strongest prognostic factor since PgR expression is activated by ER and may therefore identify a subgroup of neoplasms with greater hormone sensitivity. Likewise, PgR was the strongest predictor of response to tamoxifen inasmuch as tumors with high PgR expression under tamoxifen treatment had the lowest risk of recurrence, consistent with adjuvant data [23–26].

Our results provide further support to the contention that low-dose tamoxifen may be an effective treatment of many subjects with DIN, with an ~40% reduction of recurrences in high ER/PgR-expressing neoplasia. While recent studies indicate that the CYP2D6 genotype may be a predictor of tamoxifen efficacy [27, 28] and can therefore allow the exclusion of subjects with poor or intermediate tamoxifen-metabolizing ability, the vast majority of subjects are extensive metabolizers [29] that may well benefit from a lower dose of tamoxifen both in terms of efficacy and safety. Most notably, no difference in the frequency of endometrial cancers has so far been observed between treated and untreated subjects.

Although limited by the lack of a randomized comparison, our results support the need for a ‘preventive’ treatment intervention after surgery in women with DIN with both ER and PgR >50%. Women undergoing a conservative surgery and diagnosed with a highly hormone-responsive DIN are at increased risk of relapse in the absence of tamoxifen treatment and for this reason may benefit from tamoxifen regardless of radiotherapy and other prognostic factors. Conversely, women with low-expression PgR DIN do not seem to benefit from tamoxifen and may remain untreated or participate in clinical trials to test different compounds. A randomized definitive trial addressing these questions is warranted.

An additional limitation of our study is the absence of a systematic assessment of adverse events. Due to the observational nature of this study, tamoxifen-associated adverse events including thromboembolic events, cataracts and endometrial polyps were not accurately recorded in all women who were outside clinical trials. However, we found no difference in endometrial cancers frequencies. Moreover, the ongoing phase II trials both in pre- and postmenopausal...
women indicate no increased incidence of menopausal symptoms, endometrial polyps and deep vein thrombosis between low-dose tamoxifen and no tamoxifen [6, 11]. A phase III clinical trial in healthy postmenopausal HRT users is currently ongoing and may provide additional information about the safety and toxicity of 5 mg/day of tamoxifen in the preventive setting [30].

In conclusion, our cohort study indicates that low-dose tamoxifen is a promising strategy for highly endocrine-responsive DIN. A phase III trial comparing tamoxifen 5 mg/day versus placebo is currently ongoing in women with DIN to address this issue more definitively.

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references