Effect of Metformin on Breast Ductal Carcinoma
In Situ Proliferation in a Randomized Presurgical Trial

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Abstract

Metformin is associated with lower breast cancer risk in epidemiologic studies and showed decreased proliferation in HER2-positive breast cancer in a presurgical trial. To provide insight into its preventive potential, we measured proliferation by Ki-67 labeling index (LI) of intraepithelial lesions surrounding breast cancer. We randomly assigned 200 nondiabetic patients diagnosed with invasive breast cancer in core biopsies to metformin, 1,700 mg or placebo once daily for 28 days before surgery. Upon surgery, five to seven specimens of cancer adjacent (≤1 cm) and distant (>1 cm) tissue were screened for LCIS, ductal carcinoma in situ (DCIS), and ductal hyperplasia (DH). The prevalence of LCIS, DCIS, and DH was 4.5% (9/200), 67% (133/200), and 35% (69/200), respectively. Overall, metformin did not affect Ki-67 LI in premalignant disorders. The median posttreatment Ki-67 LI (IQR) in the metformin and placebo arm was, respectively, 15% (5–15) versus 5% (4–6) in LCIS (P = 0.1), 12% (8–20) versus 10% (7–24) in DCIS (P = 0.9), and 3% (1–4) versus 3% (1–4) in DH (P = 0.5). However, posttreatment Ki-67 in HER2-positive DCIS lesions was significantly lower in women randomized to metformin especially when ER was coexpressed: 22% (11–32) versus 35% (30–40) in HER2-positive DCIS (n = 22, P = .06); 12% (7–18) versus 32% (27–42) in ER-positive/HER2-positive DCIS (n = 15, P = .004). Eight of 22 (36%) HER2-positive DCIS were adjacent to HER2-negative invasive breast cancer. In tissue samples obtained following 4 weeks of study drug, proliferation was lower in HER2-positive DCIS for women randomized to metformin versus placebo. An adjuvant trial incorporating metformin in HER2-positive DCIS is warranted. Cancer Prev Res; 8(10); 888–94. ©2015 AACR.

Introduction

There is strong evidence that insulin resistance affects breast cancer prognosis (1), increases breast cancer risk (2), and partly explains the obesity–breast cancer risk association (3). Insulin may promote tumorigenesis via a direct effect or indirectly by affecting other modulators, such as insulin-like growth factors, sex hormones, and adipokines (4).

Metformin, a well-tolerated biguanide used as first-line treatment of diabetes, has been shown to decrease the progression from prediabetes to overt diabetes (5) and to decrease cardiovascular mortality by 25% (6). Epidemiologic studies have shown a significant risk reduction in cancer incidence and mortality among diabetic patients on metformin relative to other antidiabetic drugs and no treatment in some studies, including positive results specifically in breast cancer (7). However, a recent meta-analysis based on BMI-adjusted studies and accounting for time-related biases showed a lower magnitude of reductions in cancer incidence, albeit with retained statistical significance (8). Moreover, comparison with insulin and sulphonylureas may provide false-positive results given the putative increased risk of cancer associated with these drugs (7). In preclinical models, metformin multiple actions that contribute to anticancer effects include decreased insulin/insulin-like growth factor-1 signaling, inhibition of the mTOR, inhibition of mitochondrial complex I in the electron transport chain, and activation of AMP-activated kinase (AMPK; ref. 4).

These findings have prompted several trials of metformin as an anticancer agent, including four window of opportunity trials in breast cancer using Ki-67 as primary endpoint, with conflicting results (9–12) and an ongoing adjuvant phase III trial (13). Our presurgical trial showed a null effect overall but a heterogeneous effect with a trend to a decreased proliferation (Ki-67 LI) and apoptosis (by TUNEL) in women with insulin resistance (HOMA >2.8) and an opposite trend in women with normal insulin sensitivity (10,14). Moreover, metformin selectively decreased Ki-67 in HER2-positive (HER2+ve) cancers and in women with additional markers of insulin resistance (15). Preclinical and epidemiologic studies have suggested an effect of metformin specifically on HER2+ve tumors (16).
The field cancerization effect is well documented in breast cancer (17), and recent studies have shown that Ki-67 is positively associated with breast carcinogenesis progression (18) and prediction of subsequent breast cancer risk (19). We have previously shown the feasibility of this approach in a window of opportunity trial of lapatinib in HER2+ve breast cancer, supporting the notion that Ki-67 LI in the surrounding intraepithelial tissue may offer clues on drugs’ preventive potential (20). Here, we assessed the effect of metformin on intraepithelial proliferation adjacent to breast cancer to provide more insight into its preventive potential which has huge public health implications given the epidemic of obesity and insulin resistance in western countries.

Materials and Methods

Subjects and study design

We conducted at the European Institute of Oncology (IEO), Milan, Italy, a randomized, phase II, double-blind, placebo-controlled trial in women with stage I-IIa breast cancer candidates for elective surgery who received either metformin or placebo for 4 weeks before surgery after Institutional Review Board approval and signed informed consent (trial #S425/408, EudraCT 2008-004912-10, ISRCTN16493703). The main results on Ki-67 LI in malignant tissue have previously been published (10). The coprimary endpoint was Ki-67 LI in adjacent ductal carcinoma in situ DCIS, as previously described (20).

Treatment plan

Patients were randomly assigned to metformin, 850 mg tablets or placebo once daily on days 1 to 3 to adapt to gastrointestinal symptoms, followed by two 850 mg tablets once daily after dinner (from day 4 to 28) to minimize gastrointestinal symptoms during the daytime and to attain higher blood and tissue Cmax levels, which might be more relevant to its antitumor activity than lower steady concentrations (21). Treatment was stopped at least 48 hours before anesthesia, in keeping with FDA and National (AIFA) guidelines (22) to avoid the risk of lactic acidosis. Toxicity was evaluated using NCI-CTCAE, version 3.0.

Detection of LCIS, DCIS, and ductal hyperplasia in surgical specimens

At the time of surgical removal of the tumor, five to seven specimens of adjacent (within 1 cm from the tumor) and distant (more than 1 cm from the tumor) grossly normal tissue (i.e., the surgical margins of quadrantectomy or lumpectomy, and the grossly free quadrants from mastectomy specimens) were evaluated to assess systematically the prevalence of LCIS, DCIS, and ductal hyperplasia.

Pathology

The occurrence of ductal hyperplasia, LCIS, and DCIS was evaluated in routine hematoxylin and eosin slides. LCIS and DCIS were further subdivided according to its morphology in three histologic differentiation grades (LCIS 1, 2, and 3 and DCIS 1, 2, and 3), following WHO guidelines. For DCIS, all cases were further characterized by IHC for estrogen receptor (ER), progesterone receptor (PgR), and HER2, as previously described (23). Ki-67 LI was assessed for the present study in all intraepithelial disorders by IHC according to international recommendations and validation studies provided by a working group, including our own laboratory (24, 25), using the Mib-1 monoclonal antibody (Dako).

For each patient, one to three representative tissue sections from the initial five to seven specimens were selected by an expert pathologist and immunostained with the anti-Ki-67 antibody. Sections were mainly selected in order to obtain an amount of adjacent LCIS and DCIS tissue or distant hyperplastic cells that was adequate for Ki-67 immunostaining. We established a minimum of 500 target cells as a prerequisite for adequate measurement of the Ki-67 labeling index. If the hyperplastic, LCIS and DCIS component was enough, we limited Ki-67 staining to a single section, otherwise we used the second or the third section. The 500 target cells threshold was satisfied by evaluating one section in 65% of the cases, two sections in 26% cases, and three sections in 9% of the cases. Samples were considered representative of the duct or lobular proliferation analyzed when they contained the most represented lesion: for example, if a DCIS was composed by a grade 2 tumor with necrosis (90%), associated with a focal (10%) component of grade 1 without necrosis, we paid attention to run Ki-67 immunostaining in the two components taking into account their relative prevalence. In line with the guidelines recently issued for invasive cancer, all cases with 3+ immunoreactivity were considered positive as well as those with an equivocal (2+) HER2 immunoreactivity and an amplified reflex FISH test.

Sample size and statistical analysis

Details on power considerations and statistical analyses for the primary endpoint in cancer tissue have been provided elsewhere (10). For the coprimary endpoint Ki-67 in adjacent DCIS, we calculated post hoc that with 200 patients and a prevalence of DCIS and/or LCIS of 70%, the study had approximately 80% power to detect a 6% absolute mean difference of Ki-67 in intraepithelial neoplasia between metformin and placebo arms at surgery, a value of noticeable clinical significance as it resembles that attained by metformin in cancer tissue of insulin-resistant women (10) or tamoxifen in invasive disease (26). Main descriptive statistics for continuous data were mean and SD for normally shaped variables, median, and interquartile range for skewed variables (e.g., Ki-67 levels); independent t test or Wilcoxon rank-sum test was adopted to test for differences between arms, respectively. Absolute frequencies were reported in case of categorical data and Pearson χ2 or Fisher exact tests were used for statistical testing. A nonparametric test for trend across ordered groups (27) was used to compare Ki-67 levels with DCIS grade. Subgroup analyses were conducted testing the appropriate treatment covariate interaction term in a linear regression model, setting Ki-67 levels (log- or square root-transformed due to the skewed shape) as the response variable and treatment as explanatory dummy variable, adjusting for age and body mass index. All analyses were based on an Intention-to-Treat approach using STATA software, version 11 (StataCorp.). A two-tailed α error of 5% was taken as cutoff point for statistical significance.

Results

Overall, the prevalence of LCIS, DCIS, and ductal hyperplasia in the 200 cases was 4.5% (n = 9), 67% (n = 133), and 35% (n = 69), respectively. The main subject and tumor characteristics of the subgroup of 142 patients with intraepithelial neoplasia (LCIS or DCIS) are summarized in Table 1. All variables were evenly distributed between arms.

The distribution of median Ki-67 levels in LCIS, DCIS, and ductal hyperplasia in the two treatment arms is shown in Table 2.
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The Ki-67 LI was higher in DCIS and LCIS than in ductal hyperplasia regardless of treatment (P = 0.001), and was positively associated with DCIS grade ($P_{\text{trend}} < 0.001$, Supplementary Fig S1). There was no difference between arms on posttreatment Ki-67 LI in LCIS, DCIS (overall and by grade), or ductal hyperplasia. However, compared with placebo, Ki-67 LI was 40% lower in the metformin arm in HER2+ve DCIS, especially in those coexpressing ERs, where the relative difference was over 60%. The median and interquartile range (IQR) posttreatment Ki-67 LI in the metformin and placebo arms was, respectively, 22% (11–32) versus 35% (30–40) in all HER2+ve DCIS ($P = 0.06$); 12% (7–18) versus 32% (27–42) in ER+ve/HER2+ve DCIS ($P = 0.004$); 18% (12–18) versus 32% (24–44) in PgR+ve/HER2+ve DCIS ($P = 0.02$). The distribution of Ki-67 LI in DCIS by HER2 and hormone receptor status in the two arms is illustrated in Fig. 1. Interestingly, the prevalence of HER2+ve DCIS was 50% higher than invasive disease, in as much as all 14 HER2+ve DCIS that were adjacent to invasive cancers under metformin, this corresponds to a lower proliferation in the DCIS component after treatment. Given the lack of tumor adjacent DCIS tissue in the pretreatment biopsies, which typically sample the tumor core, we further analyzed the frequency distribution of DCIS grade in HER2+ve cancer tissue to exclude an uneven distribution between arms. Of the 10 cases in the placebo arm, none was grade 1 DCIS, four (40%) were grade 2, and six (60%) were grade 3; of the 12 women in the metformin arm, two (17%) were grade 1 DCIS, four (33%) were grade 2, and six (50%) were grade 3 without: difference between arms ($P = 0.4$). A double-immunostaining picture displaying HER2 (brown) and Ki-67 (red) immunoreactivity in a case with HER2–ve DCIS, but there were eight additional cases of HER2+ve DCIS that were adjacent to the HER2–negative (HER2–ve) breast cancers (Table 3). There was no evidence for a different effect in the metformin arm versus the placebo arm on posttreatment Ki-67 in DCIS by HOMA index in all women ($n = 141$, $P_{\text{interaction}} = 0.7$, data not shown). However, in the 14 women with HER2+ve DCIS and HOMA index $\geq$ 2.8, the median Ki-67 was 32 (32–40) on placebo and 26.5 (18–30.5) on metformin, whereas in the 8 women with HOMA index $\geq$ 2.8, the median Ki-67 was 38 (30–40) on placebo versus 7 (2–71) on metformin. Although this finding is based on eight cases only, three of which were on metformin (Ki-67 was 2, 7, and 71 respectively), the interaction test was not significant ($P = 0.3$), the difference in Ki-67 between arms is striking.

The congruence of findings between the cancer adjacent DCIS and invasive components is reported in Fig. 2. In most cases where there appears to be a significant decrease in proliferation in invasive cancers under metformin, this corresponds to a lower proliferation in the DCIS component after treatment. Given the lack of tumor adjacent DCIS tissue in the pretreatment biopsies, which typically sample the tumor core, we further analyzed the frequency distribution of DCIS grade in HER2+ve cancer tissue to exclude an uneven distribution between arms. Of the 10 cases in the placebo arm, none was grade 1 DCIS, four (40%) were grade 2, and six (60%) were grade 3; of the 12 women in the metformin arm, two (17%) were grade 1 DCIS, four (33%) were grade 2, and six (50%) were grade 3 without: difference between arms ($P = 0.4$). A double-immunostaining picture displaying HER2 (brown) and Ki-67 (red) immunoreactivity in a case with HER2+ve DCIS and the corresponding invasive cancer is illustrated in Fig. 3. The levels of Ki-67 in the 22 subjects with HER2+ve adjacent DCIS and the corresponding invasive cancer are depicted in Supplementary Table S1.

There was no effect of metformin on Ki-67 LI in ductal hyperplasia overall (Table 2). However, there was a lower proliferation

### Table 2. Median (IQR) of Ki-67 LI (%) in premalignant disorders by treatment arm

<table>
<thead>
<tr>
<th>Premalignant group</th>
<th>Metformin arm</th>
<th>Placebo arm</th>
<th>$P$</th>
<th>$P_{\text{interaction}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCIS ($n = 95$, 9%)</td>
<td>5 (5–15) n = 5</td>
<td>5 (4–6) n = 4</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Ductal hyperplasia ($n = 69$, 35%)</td>
<td>3 (1–4) n = 33</td>
<td>3 (1–4) n = 36</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>All DCIS ($n = 133$, 67%)</td>
<td>10 (8–20) n = 66</td>
<td>10 (7–24) n = 67</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>DCIS grade 3 ($n = 24$)</td>
<td>33 (25–55) n = 14</td>
<td>40 (32–40) n = 10</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>DCIS grade 2/2 ($n = 109$)</td>
<td>10 (7–16) n = 52</td>
<td>10 (6–17) n = 57</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>HER2+ve ($n = 32$)</td>
<td>22 (11–32) n = 12</td>
<td>35 (30–40) n = 10</td>
<td>0.06</td>
<td>0.04</td>
</tr>
<tr>
<td>HER2–ve ($n = 58$)</td>
<td>16 (10–20) n = 31</td>
<td>17 (8–26) n = 27</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>ER+ve/HER2+ve ($n = 15$)</td>
<td>12 (7–18) n = 7</td>
<td>32 (27–42) n = 8</td>
<td>0.004</td>
<td>0.001</td>
</tr>
<tr>
<td>ER+ve/HER2–ve ($n = 43$)</td>
<td>16 (10–20) n = 30</td>
<td>15 (8–22) n = 23</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>ER–/PR+ve/HER2+ve ($n = 12$)</td>
<td>18 (12–18) n = 5</td>
<td>32 (24–44) n = 7</td>
<td>0.02</td>
<td>0.05</td>
</tr>
<tr>
<td>ER–/PR+ve/HER2–ve ($n = 48$)</td>
<td>16 (10–20) n = 27</td>
<td>12 (8–20) n = 21</td>
<td>0.6</td>
<td></td>
</tr>
</tbody>
</table>

$^1$Wilcoxon rank-sum test.

$^2$From linear regression modeling, setting Ki-67 levels as the response variable and treatment as explanatory dummy variable, adjusting for age and body mass index.
Metformin and Breast Intraepithelial Proliferation

fraction in women with abdominal adiposity (waist/hip girth ratio > 0.85) in the metformin arm ($P_{\text{interaction}} = 0.05$).

**Discussion**

Window of opportunity, presurgical models are being used to screen the therapeutic activity of candidate agents and characterize their mechanism of action (29). These studies often use tumor Ki-67 as the main surrogate biomarker in as much as the decrease in this proliferation-related antigen after short-term presurgical hormonal treatment has prognostic significance on progression-free and overall survival in several studies (26, 30, 31). For instance, we showed (26) that a 3% absolute decrease in Ki-67 was associated with a 15% relative decrease of invasive recurrence and a nearly 18% decrease of death.

The presurgical model may also provide insight into the drug's preventive effect on tumor adjacent dysplastic (or intraepithelial neoplastic) cells and distant ductal hyperplastic cells resulting from the field cancerization effect, which is well documented in breast cancer (17). Recent studies have shown that Ki-67 LI is positively associated with progression of precursor lesions (18, 32), and its level of staining in core biopsies of atypical precursor lesions may predict subsequent breast cancer risk (19). Modulation of Ki-67 LI in breast fine needle aspirates from high-risk women has also been used to test the activity of preventive agents (33).

Our recent presurgical trial indicated complex effects of metformin on cancer tissue proliferation with a 3% decrease of Ki-67 LI in insulin-resistant women (HOMA > 2.8) and an opposite trend in women with normal insulin sensitivity (10). Moreover, metformin selectively decreased Ki-67 LI in HER2+ve cancers and in women with additional markers of insulin resistance (15). In the present study, we show the high prevalence of the field cancerization effect, with a 70% prevalence of intraepithelial neoplastic lesions in tissue surrounding invasive cancers, supporting the notion that the presurgical model may be a cost effective model to screen agents with preventive potential. Our data indicate a remarkable 13% median absolute difference of post-treatment Ki-67 LI in adjacent HER2+ve DCIS in the metformin arm compared with placebo, which rose to 20% in those coexpressing ER. A lower Ki-67 was remarkable in women with HER2+ve DCIS and HOMA index > 2.8 under metformin, in line with our prior observation in invasive cancer (10), although this finding was based on eight cases only. These results extend and further complement our prior findings in HER2+ve invasive disease, where metformin significantly reduced the Ki-67 increase observed in the placebo arm after 4 week between biopsy and surgery (15, 34). In addition, the number of adjacent HER2+ve DCIS was larger than that of HER2+ve invasive cancer, in line with prior data (35), indicating that our findings do not simply replicate results in HER2+ve invasive disease (15). Indeed, the large magnitude of the posttreatment Ki-67 difference between arms strongly suggests that HER2+ve DCIS is particularly sensitive to the antiproliferative effect of metformin, which has important preventive implications because HER2 overexpression or gene amplification is involved in the transition from DCIS to invasive disease (36) and predicts the presence of invasive foci (37).

Although our findings are the result of a subgroup analysis and need further confirmation, they are biologic plausible and provide strong justification for an adjuvant trial of metformin after surgical excision of DCIS. The treatment of HER2+ve DCIS after surgical excision is a recognized unmet medical need (38). Women with HER2+ve DCIS with Ki-67 of 10% or higher had a 47% risk of local recurrence at 10 years with excision alone versus 24% with excision and radiotherapy (39). Tamoxifen is only partially effective in ER+ve/HER2+ve DCIS and the 5-year risk of recurrent ranges between 10% to 15% in HER2+ve DCIS or with Ki-67 $>$14% (40, 41). Moreover, Ki-67 levels greater than 14% predict the efficacy of radiotherapy (41). The NSABP B-43 is a phase III trial currently underway testing the efficacy of intravenous trastuzumab in addition to radiotherapy in HER2+ve DCIS (42). A pilot study of HER2 vaccination in HER2+ve DCIS has also provided promising results (43). The full results of trial NRG Oncology/NSABP B-35 recently presented at ASCO (44) and of IBIS-II, both comparing tamoxifen to anastrazole in women with DCIS, will probably shed light into the effect of aromatase inhibitors in HER2+ve/ER+ve DCIS.

Table 3. Association between HER2 status in invasive breast cancer and adjacent DCIS

<table>
<thead>
<tr>
<th>HER2 status in invasive cancer</th>
<th>HER2 status in DCIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative (n = 58)</td>
<td>Positive (n = 22)</td>
</tr>
<tr>
<td>Negative (n, %)</td>
<td>58 (100)</td>
</tr>
<tr>
<td>Positive (n, %)</td>
<td>8 (36)</td>
</tr>
<tr>
<td>Positive (n, %)</td>
<td>0 (-)</td>
</tr>
<tr>
<td>Positive (n, %)</td>
<td>14 (64)</td>
</tr>
</tbody>
</table>

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in a window of opportunity trial that the dual HER2 inhibitor lapatinib decreased Ki-67 LI in the surrounding HER2 +ve DCIS to the same extent as in invasive tissue, providing the rationale for an adjuvant study of lapatinib in DCIS (20). A much lower dose of lapatinib given after meal has been advocated as a cost effective and better tolerated way to use this oral anti-HER2 + agent (45), particularly in early disease stage such as in DCIS. Our current findings might even support an adjuvant trial of low-dose lapatinib plus metformin in HER2 +ve DCIS, with the addition of hormone therapy in ER +ve/HER2 +ve DCIS. This combination treatment might represent a simple and economic approach to this disease.

In vivo, metformin is able to induce downregulation of HER1 and HER2, and in vitro the drug inhibits self-renewal and proliferation of cancer stem cells in HER2-overexpressing breast cancer cell (46) and to selectively target tumor-initiating cells in HER2-overexpressing breast cancer models. A neoadjuvant clinical trial testing the activity of metformin and trastuzumab in HER2 +ve breast tumors is underway (47).

Our data also seem to suggest a lower Ki-67 LI in ductal hyperplasia under metformin in women with abdominal obesity, the hallmark of insulin resistance, in line with our findings in cancer tissue (10, 15). Although a false-positive finding cannot be excluded, our observations further characterize metformin as a targeted agent based on specific host (insulin resistant) and tumor (HER2 +ve) characteristics. In preclinical models, metformin inhibits the inflammatory response associated with cellular transformation and breast cancer stem cell growth, whereas it is ineffective in noninflammatory cell lines (48). As metformin

![Figure 2. Dotplots of Ki-67 labeling index in the three data points (pretreatment invasive, posttreatment invasive, and posttreatment DCIS) from each of the 22 cases with cancer adjacent HER2 + ve DCIS by allocated arm. All HER2 + ve DCIS (top); ER + ve/HER2 + ve DCIS (bottom). Horizontal solid lines represent median values; horizontal dashed lines represent 25th and 75th percentiles. P values by Mann-Whitney U test.](cancerpreventionresearch.aacrjournals.org)
 alters energy metabolism, it may block a metabolic stress response that stimulates the inflammatory pathway associated with insulin resistance, including those with breast adipose inflammation (49).

Our study has two important limitations: (i) the lack of a pretreatment Ki-67 level of DCIS and other intraepithelial lesions, which prevents a more powerful pre- and post-treatment comparison. Unfortunately, obtaining adjacent tissue during a pre-treatment biopsy of cancer tissue raises significant practical issues, which usually limit the procurement of a baseline DCIS tissue adjacent to cancer; (ii) the effect of metformin was noted only in the subgroup of HER2+ve DCIS, which is biologically plausible but has exploratory significance and needs confirmation in future studies.
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