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Late cutaneous effects of a local potent steroid during adjuvant radiotherapy for breast cancer

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ABSTRACT

Purpose: The aim of this study was to evaluate whether treatment with a local potent corticosteroid during adjuvant external radiotherapy (ERT) of breast cancer is associated with late skin toxicity.

Material and methods: Sixty patients (32 treated with potent corticoid cream versus 28 controls treated with moisturizer) who had been included in a randomized study on prophylactic local corticosteroid treatment under adjuvant ERT in 2009 and 2010 were subjected to a follow-up study in 2016.

Assessments of skin texture were registered according to the Late Radiation Morbidity Scoring Scheme (RTOG). Dryness, skin colour and skin thickness were objectively measured using non-invasive instruments. The patients were assessed for differences between their treated and untreated breasts.

Results: Skin atrophy was not noticed in any of the 60 patients. Objective instrumental measurements did not reveal any significant differences in skin dryness, colour, pigmentation or skin thickness over the average follow-up time of six years. Clinical assessment based on the RTOG scoring system revealed that the odds ratio of having late skin problems in patients treated with moisturizer compared to patients treated with corticosteroid was 3.2 (95% CI: 1.0–10.1). Patients reported minor cosmetic dermatological sequelae. Seven patients developed telangiectasia, which caused cosmetic inconvenience.

Conclusion: In this study, prophylactic corticosteroid treatment to ameliorate radiation dermatitis during adjuvant ERT of breast cancer was not associated with an increase in late skin toxicity nor did it result in skin atrophy. This study is limited by its small sample size, and the risk for false positive findings.

Introduction

Adjuvant external radiotherapy (ERT) is an essential component of breast cancer treatment. However, ERT often causes acute, consequential late or chronic skin reactions [1–3]. Acute toxicity manifesting as redness, dryness, desquamation and moist desquamation within the treated skin area develops within the first weeks of ERT [4]. The onset of chronic skin reactions has a long latency from months to several years after ERT [1]. Skin atrophy, fibrosis, changes in pigmentation, telangiectasia and skin cancer can develop [5]. The incidence of long-term adverse effects on the skin varies from 5 to 30% for fibroses and telangiectasia [6].

There is no clear cut association between the degree of radio dermatitis and the development of late reactions [7]. However, moist desquamation has been shown to be correlated with the development of telangiectasia but did not influence the extent of fibrosis [8]. Many studies have shown that prophylactic treatment with a potent corticosteroid cream ameliorates acute radio dermatitis [9–12]. However, long-term local safety, especially the development of skin atrophy, is an issue of concern [13]. To our knowledge, no studies have assessed the long-term skin effects of corticosteroid treatment administered in parallel with ERT.

The aim of this study was to evaluate whether treatment with a local potent corticosteroid during adjuvant ERT of breast cancer is associated with late skin toxicity.
Material and methods

The study was performed from September 2016 to December 2016. Patients treated with ERT for breast cancer in 2009 and 2010 were invited to participate. They had been included in a randomized study on prophylactic local treatment using either a potent corticosteroid (betamethasone 0.1%) or a moisturizer (brand name Essex) [14]. Patients underwent adjuvant ERT with 50 Gy/25 fractions after initial mastectomy or breast-preserving surgery. In some patients, the radiation field was extended to the armpit and the supraclavicular fossa. Patients who had undergone mastectomy received a 3 cm marginal bolus around the scar. When the bolus was used, patients received 105–110% of the scheduled dose corresponding to the volume beneath the bolus of 55 Gy/25 fractions. Patients younger than 40 years of age and patients who underwent a surgery that was not radically performed were given a boost of 16 Gy/8 fractions, according to national guidelines [15]. Acute radiodermatitis was assessed by using the Radiation Morbidity Scoring Scheme from the Radiation Toxicity Oncology Group (acute RTOG) at the end of ERT. This scoring system ranks dermatitis signs from minor signs (grade 1) to severe signs (grade 4). Acute RTOG was stratified into two groups: 0–1 (mild) and 2–3 (severe).

Out of 102 patients participating in the original study, 42 were not included in the present study due to the following reasons: 14 had died (10 due to metastatic disease of internal organs, one due to loco-regional recurrence and pulmonary metastases, and three due to other diseases), seven did not respond after contacting, five were included in the present study. All patients obtained a study information letter and thereafter were asked by phone to participate. Twelve (10 due to metastatic disease of internal organs, one due to loco-regional recurrence and pulmonary metastases, and one due to other diseases) refused to participate. Thus, 60 patients were included in the present study. The study was conducted in accordance with the protocol, regulatory requirements, and ethical principles of the Ethical Products Agency (EudraCT 2009-018059-18) prior to the inclusion of patients. The study protocol, patient information and consent forms were reviewed and approved by the Regional Ethics Committee no. 2014/449-32 at the Linköping University and by the Swedish Medical Products Agency (EudraCT 2009-018059-18) prior to the inclusion of patients. The study was conducted in accordance with the protocol, regulatory requirements, and ethical principles of the national guidelines.

Table 1

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>Corticosteroid</th>
<th>Moisturizer</th>
<th>Total number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study population</td>
<td>28</td>
<td>32</td>
<td>60</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>67 (42–75)</td>
<td>65 (33–80)</td>
<td></td>
</tr>
<tr>
<td>Surgical procedures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mastectomy, modified</td>
<td>9</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>Breast preserving surgery ERT</td>
<td>19</td>
<td>22</td>
<td>41</td>
</tr>
<tr>
<td>Chest wall with bolus</td>
<td>9</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>Whole breast</td>
<td>19</td>
<td>22</td>
<td>41</td>
</tr>
<tr>
<td>Supplementary armpit and supraclavicular fossa</td>
<td>9</td>
<td>8</td>
<td>17</td>
</tr>
<tr>
<td>Chemotherapy before ERT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without chemotherapy</td>
<td>15</td>
<td>22</td>
<td>37</td>
</tr>
<tr>
<td>FEC every third week x 3, and</td>
<td>13</td>
<td>10</td>
<td>23</td>
</tr>
<tr>
<td>paclitaxel weekly x 12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocrine therapy after ERT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen or/and aromatase inhibitors</td>
<td>23</td>
<td>21</td>
<td>44</td>
</tr>
</tbody>
</table>

Statistics

Descriptive statistics were used to describe the patient population. Paired t-tests were used to evaluate differences in skin characteristics between treated and untreated breast, for which each treated patient also served as her own control. For differences in treatment with steroid or moisturizer, t-tests were performed on the group level. A p-value ≤0.05 was considered statistically significant.

Ethic

The study protocol, patient information and consent forms were reviewed and approved by the Regional Ethics Committee no. 2014/449-32 at the Linköping University and by the Swedish Medical Products Agency (EudraCT 2009-018059-18) prior to the inclusion of patients. The study was conducted in accordance with the protocol, regulatory requirements, and ethical principles of the
Table 2
Dryness, redness, pigmentation and skin thickness characteristics and differences in dryness, redness, pigmentation and skin thickness after ERT in combination with treatment with a potent steroid compared to a moisturizer.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Corticosteroid treated breast (mean)</th>
<th>Moisturizer treated breast (mean)</th>
<th>Difference moisturizer - corticosteroid (mean)</th>
<th>p-Value</th>
<th>Healthy breast (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dryness, (Capacitance)</td>
<td>69.6</td>
<td>65.2–74.0</td>
<td>66.9–73.2</td>
<td>0.44</td>
<td>69.9</td>
</tr>
<tr>
<td>Redness colorimeter (a')</td>
<td>10.6</td>
<td>9.4–11.8</td>
<td>9.0–10.8</td>
<td>0.19</td>
<td>9.9</td>
</tr>
<tr>
<td>Pigmentation colorimeter (L)</td>
<td>29.5</td>
<td>28.4–30.6</td>
<td>28.4–31.0</td>
<td>0.3</td>
<td>29.0</td>
</tr>
<tr>
<td>Skin thickness (mm) ultrasound</td>
<td>1.28</td>
<td>1.17–1.39</td>
<td>1.12–1.29</td>
<td>0.19</td>
<td>1.17</td>
</tr>
</tbody>
</table>

Discussion

The present study identified no long-term sequelae following six weeks of local corticosteroids used prophylactically to ameliorate radio dermatitis during adjuvant ERT in breast cancer patients. The development of skin atrophy is of particular concern as corticosteroids used for months or years, locally or systemically, are known to result in atrophy of the skin [22]. General fear of skin atrophy may explain the unwillingness of physicians and patients to use corticosteroid cream to prevent ERT dermatitis [23]. Studies of normal skin of healthy volunteers exposed to a potent local corticosteroid for six weeks have shown that the skin becomes thinner but the reduction of skin thickness, amounting to approximately 15%, returns to normal a few weeks after discontinuation of the corticosteroids [22]. In our previous report, corticosteroids were used for six weeks to prevent radio dermatitis.

In this study, clinical assessments via RTOG showed that one-third of patients had minor late sequelae, such as slight fibrosis, changes in pigmentation and telangiectasia, which mainly occurred in the group treated with the moisturizer compared to the group treated with corticosteroid with an odds ratio 3.2 (95% CI: 1.0–10.1). Patients treated with moisturizer during ERT who developed severe acute skin reactions experienced more late skin sequelae compared to those treated with corticosteroid. Thus, short course corticosteroid treatment during adjuvant ERT might also have a protective effect against late sequelae. Future studies should confirm this finding.

The cosmetic outcome of patients treated with breast-conserving surgery and ERT appeared to be favourable, as half of the patients did not report any differences between the treated and untreated breast. On the other hand, in the group that underwent mastectomy, seven patients out of 21 developed telangiectasia, which was visible and disturbing to them. Earlier publications have shown that the development of telangiectasia due to radiation is more common in patients with acute radiodermatitis with moist desquamation (acute RTOG grade 3) and radiation dose [6,8]. All patients with telangiectasia had an acute RTOG score of 2–3 and had received a bolus.

A follow-up time of six years seems to be an adequate observation period [24]. In a study by Bentzen, [25] the length of time to the expression of 90% of the final frequency of moderate to severe complications was 3.2 years for fibrosis and 4.7 years for telangiectasia.

Table 3
Comparison of acute and late RTOG assessments.

<table>
<thead>
<tr>
<th></th>
<th>Late RTOG grade 0</th>
<th>Late RTOG grade &gt; 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute RTOG grade 0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Acute RTOG grade 1</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Acute RTOG grade 2</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>Acute RTOG grade 3</td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>
The sample we studied is of limited size, and thus, we cannot exclude an effect of local corticosteroid on the direction of cutaneous sequelae. The use of quantitative measurements to depict subtle effects did not detect any tendency towards atrophy. In conclusion, it remains unlikely that prophylactic corticosteroid treatment to ameliorate acute radio dermatitis during adjuvant ERT of breast cancer has any clinically relevant adverse effects on late skin reactions.

References