Local $\alpha$-Tocopherol for Acute and Short-Term Vaginal Toxicity Prevention in Patients Treated With Radiotherapy for Gynecologic Tumors

Andrea Galuppi, MD, Anna Myriam Perrone, MD, PhD, Mariangela La Macchia, MD, Donatella Santini, MD, Serena Medoro, MD, Lucia Ricci Maccarini, MD, Isabella Strada, MD, Federica Pozzati, MD, Martina Rossi, MD, and Pierandrea De Iaco, MD
Local α-Tocopherol for Acute and Short-Term Vaginal Toxicity Prevention in Patients Treated With Radiotherapy for Gynecologic Tumors

Andrea Galuppi, MD,* Anna Myriam Perrone, MD, PhD,† Mariangela La Macchia, MD,* Donatella Santini, MD,‡ Serena Medoro, MD,* Lucia Ricci Maccarini, MD,† Isabella Strada, MD,† Federica Pozzatti, MD,† Martina Rossi, MD,† and Pierandrea De Iaco, MD†

Introduction: Data in literature about the use of adjuvant treatment to reduce acute adverse effects of radiotherapy on the pelvis are scant, with the exception of a few reports on the topical use of estrogen, which promotes proliferation of epithelium.

Materials and Methods: In this prospective trial, α-tocopherol acetate was topically administered to patients affected by endometrial and cervical cancer and undergoing radiation treatment to avoid acute vaginal complications.

Results: Vaginal application of α-tocopherol reduced vaginal toxicity and pain, although vaginal secretion was not significantly different in the 2 groups studied. The histological scoring system showed a significant reduction of inflammation, no difference in fibrosis, and an increase of anacanthosis.

Conclusions: The use of α-tocopherol as adjuvant treatment to reduce the acute adverse effects of radiotherapy on the vagina should be considered.

Key Words: α-Tocopherol acetate, Vaginal toxicity, Radiotherapy, Endometrial cancer, Cervical cancer

Received April 6, 2011, and in revised form May 5, 2011.
Accepted for publication May 8, 2011.

(Int J Gynecol Cancer 2011;21: 1708–1711)

Radiation therapy (RT) represents an important therapeutic component in the management of many gynecologic malignancies and is used as either definitive or adjuvant therapy after surgery. Epidemiologic analysis suggests that this therapy is indicated for 60% of cervical cancer (CC) patients, and 45% of endometrial cancer (EC) patients.1–2

Late toxicity after radiotherapy on the pelvis for gynecological neoplasias is observed in 18% to 32% of patients,3 where acute genitourinary toxicity is present in 75% of patients. Patient quality of life is consequently hampered by radiotherapy, both physically and psychologically.4 Complications of vaginal irradiation are vaginal secretion, bleeding, pain, and the onset of vaginal stenosis with subsequent psychological and local sequelae.5 In fact, after radiotherapy, fibrosis and atrophy in samples of normal tissue are not uncommon.3

With the exception of a few reports on the topical use of estrogen, which promotes proliferation of epithelium,6 data in literature about the use of adjuvant treatments to reduce acute adverse effects of radiotherapy on the pelvis are scant. Dale et al7 observed that comedication with hydrolytic enzymes reduced the incidence of acute vaginal toxicity, from a mean score of 0.85 to 0.55, without reaching statistical significance.

The use of antioxidants during radiotherapy has long been controversial. Antioxidants are known for their ability to scavenge free radicals, potentially reducing the damage caused by ionizing radiation to treated tissue.8 The effectiveness of α-tocopherol acetate may be explained not only by structural features but also by functional
interaction with retinoids, as suggested by studies in which α-tocopherol acetate for systemic use reduces the toxic effects of 13cis-retinoic. The idea of using the α-tocopherol acetate for topical treatment rests on the following evidence: the redox chemistry of the vitamin, compatible with an antioxidant effect in vivo, the hydrolysis of the ester in the skin, and thus the prodrug nature of the acetate.

The aim of our study was to evaluate the protective effects of vitamin E topically administered to patients undergoing radiation treatment of EC and CC to avoid vaginal complications.

**PATIENTS AND METHODS**

Patients with EC and CC treated with primary surgery and candidate for adjuvant radiotherapy were enrolled in our study. This was an open-label study. The trial was approved by the local ethics committee. Patients eligible for the study were assigned to receive 1 suppository of 500-mg α-tocopherol acetate intravaginally (Filmene gyno: HUIKA srl, Rovigo, Italy) daily from the first day of radiation treatment until 60 days after completion of RT (group A) and no treatment (group B).

Radiotherapy was performed by a combination of external irradiation and intracavitary brachytherapy. Patients received 45 to 46 Gy of whole-pelvis radiotherapy with 18-MV x-rays using 4-field shaped beams. The daily fraction was 1.8 to 2.0 Gy, with 5 fractions weekly. Patients submitted to pulsed dose rate of intracavitary brachytherapy received 32 to 35 Gy (0.70 Gy dose/pulse).

Acute toxicity of the mucosa was assessed using the Radiation Therapy Oncology Group scoring system (score 0–4); where 0 zero indicates normal mucosa; 1, mild mucositis; 2, moderate mucositis; 3, severe mucositis; and 4, vaginal ulceration or necrosis. Vaginal secretions were evaluated with a 0 to 3 score; where 0 is no secretions; 1, serous secretions; 2, serous-hemorrhagic secretions; and 3, hemorrhagic secretions. Pain was assessed by reference to the visual analog scale considering a scale of 0 to 10; where 0 is no pain and 10 is maximum imaginable pain. All subjective and objective evaluations were performed at different times: time 0 (T0) indicates the beginning of external radiation treatment; time 1 (T1), the last day of brachytherapy; time 2 (T2), 60 days after completion of radiation treatment. Patients in group A were subjected to biopsy of vaginal mucosa at T0, T1, and T2; patients in the control group underwent vaginal biopsy at T2. Biopsy specimens were obtained by punch biopsy at the upper third of the vagina. Vaginal specimens were fixed in 4% formaldehyde and were sent to a pathology laboratory for histological analysis. The presence and intensity of inflammation, acanthosis, and fibrosis were assessed microscopically using histological criteria and evaluated with a 0 to 3 score; where 0 indicates no alteration; 1, mild alteration; 2, moderate alteration; and 3, severe alteration.

All continuous data are expressed as mean and SD of the mean and range. An unpaired t test was performed to investigate variable differences between the groups.

Pearson χ² test, calculated by the Monte Carlo method, was performed to investigate the relationship between group variables. For all tests, P < 0.05 was considered significant. Statistical analysis was carried out by means of the Statistical Package for the Social Sciences software version 9.0 (SPSS, Inc, Chicago, IL).

**RESULTS**

From June 2005 to January 2009, we enrolled 62 patients in the study: 33 in group A and 29 in group B. The characteristics of these patients are summarized in Table 1. There were no statistically significant differences in age and postsurgical stage between the 2 groups. Mean doses of radiotherapy treatment were homogeneously distributed in the 2 groups (Table 1).

Mean duration of treatment was 48 ± 3.7 and 45 ± 6.4 days in groups A and B, respectively. Patients in the research group received α-tocopherol acetate intravaginally for 108 ± 10.5 days (mean ± SD). All patients completed the treatment.

Histologic diagnosis was obtained in all patients (groups A and B). Results of local toxicity, vaginal secretion, pain, and histological details are listed in Table 2. No differences were found between the 2 groups regarding vaginal toxicity, secretions, and pain in T0. We found a significant increase of local toxicity in T1 and in T2 in group B versus group A (P < 0.001). In fact, severe local toxicity (scores 3 and 4) was present in 2 (6%) of 33 patients in group A and in 15 (52%) of 29 patients in group B, and at T2, severe local toxicity was observed in 2 patients (6%) in the treatment group and in 7 patients (24%) in the control group. Vaginal pain was reduced in the study group at T1 and at T2, without reaching any statistical significance. No differences were detected in vaginal secretion. The histological scoring system

**TABLE 1.** Population characteristics, stage of EC and CC, and dose of radiotherapy received

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), yr</td>
<td>67 (12.3)</td>
<td>66 (13.6)</td>
<td>NS</td>
</tr>
<tr>
<td>EC patients, n (%)</td>
<td>15 (46)</td>
<td>14 (48)</td>
<td>NS</td>
</tr>
<tr>
<td>CC patients, n (%)</td>
<td>18 (54)</td>
<td>15 (52)</td>
<td>NS</td>
</tr>
<tr>
<td>Pathologic stage, n (%)</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>EC IC</td>
<td>11 (73)</td>
<td>9 (64)</td>
<td>NS</td>
</tr>
<tr>
<td>EC IIB</td>
<td>3 (20)</td>
<td>4 (29)</td>
<td>NS</td>
</tr>
<tr>
<td>EC III</td>
<td>1 (7)</td>
<td>1 (7)</td>
<td>NS</td>
</tr>
<tr>
<td>CC IB</td>
<td>18 (100)</td>
<td>15 (100)</td>
<td>NS</td>
</tr>
<tr>
<td>EBRT, mean (SD), Gy</td>
<td>45.5 (0.5)</td>
<td>45.9 (2.8)</td>
<td>NS</td>
</tr>
<tr>
<td>BRT, mean (SD), Gy</td>
<td>6.2 (7.4)</td>
<td>7.5 (9.5)</td>
<td>NS</td>
</tr>
</tbody>
</table>

EBRT, Intracavitary brachytherapy; BRT, combination of external irradiation and intracavitary brachytherapy; NS, not significant.
showed a significant reduction in $T_2$ of vaginal inflammation and an increase of vaginal acanthosis ($P < 0.05$). No differences were detected in vaginal fibrosis.

## DISCUSSION

Our preliminary analysis showed that vaginal application of α-tocopherol reduces vaginal toxicity and pain, although vaginal secretion was not significantly different in the 2 groups. The histological scoring system showed a significant reduction of inflammation, no difference in fibrosis, and an increase of acanthosis.

To our knowledge, this is the first study on the use of α-tocopherol as an adjuvant treatment to reduce the acute adverse effects of radiotherapy on the vagina.

Radiotherapy is associated with cellular damage and subsequent inflammation, erythema, moist desquamation, and a confluent mucositis, particularly in the area of contact with brachytherapy sources. Thin, filmy adhesions or synechiae become permanent if not managed appropriately. Acute radiation vaginitis is managed with vaginal douching and topical intravaginal estrogen. Estrogens stimulate epithelial regeneration, but there are some patients who cannot take steroids and will have vaginitis unresponsive to topical estrogen.

Our study shows that local administration of α-tocopherol can be a good adjuvant in the reduction of acute vaginal toxicity during radiotherapy and could represent an alternative for those patients in whom the use of estrogens is contraindicated or not effective.

A direct effect of the inflammation is the formation of adherences between the vaginal walls commonly at the upper third level that obliterates either totally or partially access to the cervix or the vaginal dome. Such obliteration is harmful for 2 important reasons: (1) it limits oncological follow-up by hiding possible recidivists and (2) it inhibits sexual relations with consequent reduction of quality of life and psychological well-being. The daily application of α-tocopherol enables the reduction of adhesions through 2 mechanisms: (1) it reduces inflammatory reaction (Table 2) and (2) it lubricates the vaginal walls with an increase of trophism shown by the increase of acanthosis (Table 2).

Although this type of treatment can reduce pain, inflammation, and adherences, it does not seem to affect the fibrosis resulting from the effects of long-term radiotherapy and, in particular, the brachytherapy, represented by stenosis of the vagina, which inhibits sexual relations, and for this type of problem, the only currently available remedy seems to be dilative therapy.

There is no reliable evidence to show that routine regular vaginal dilation during or after radiotherapy prevents the late effects of radiotherapy or improves quality of life. However, it is also plausible that persistently interfering with the vagina during the inflammatory phase of radiotherapy treatment might cause additional scarring and promote additional damage, both physically and psychologically.

Our preliminary study showed that treatment with α-tocopherol is well tolerated because all patients completed the treatment with no dropouts.

Radiotherapy on the pelvis can significantly alter the quality of vaginal tissue, future possibility of intercourse, and follow-up. Vaginal treatment with α-tocopherol could be an alternative for improvement in the consequences of radiotherapy. Further studies and experiments on other substances are necessary to reduce the acute effects of radiotherapy and to improve the quality of life of these patients.

## REFERENCES

5. Johnson N, Miles TP, Cornes P. Dilating the vagina to


