Radiation recall effect with docetaxel: Is it a barrier for sandwich approach of radiotherapy sequencing in adjuvant breast cancer treatment?

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In recent years new developments occurred in adjuvant therapy of breast cancer. The role of radiotherapy and taxanes increased with the insight of new studies. However, we observed an unexpected high incidence of radiation recall phenomenon with the sandwich approach of administering radiotherapy between anthracyclin based chemotherapy and docetaxel for the patients with more than 3 positive axillary nodes. Here, we report three cases with radiation recall and discuss the phenomenon in the context of taxanes. [Turk J Cancer 2001;31(2):82-86]

Key words: Radiation recall, dermatitis, docetaxel, radiotherapy, breast cancer

In last 3 years new developments occurred in adjuvant breast cancer treatment. Although there are some studies, claiming that adjuvant radiotherapy only improves local control without effect on survival, in two recent studies from Denmark and Canada it was shown that a survival advantage may be achieved in patients with positive axillary nodes (1,2). Furthermore, in the interim analysis of Intergroup-0148 study, adding paclitaxel after standard cyclophosphamide/adriamycin (AC) increased both disease free and overall survival (3). Based on these studies, an additional 4 cycles of taxanes including paclitaxel or docetaxel have been started to be administered for the patients with more than 3 positive axillary nodes, after the anthracyclin based adjuvant chemotherapy and locoregional radiotherapy. However, we observed an unexpected high incidence (3 out of first 18 patients) of radiation recall phenomenon with the sandwich approach of administering radiotherapy between anthracyclin based chemotherapy and docetaxel for the patients with more than 3 positive axillary nodes. Here we present these 3 patients in whom docetaxel was administered shortly after radiotherapy and discuss possible consequences considering timing of adjuvant radiotherapy in breast cancer.
Cases

Characteristics of 3 patients treated with sequential protocol and experiencing a radiation recall phenomenon were presented in table 1.

<table>
<thead>
<tr>
<th>Patient characteristics and radiation recall</th>
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<tbody>
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<td><strong>Case 1</strong></td>
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<td>Histology</td>
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<td>ER/PR</td>
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<td>c-Erb-B2</td>
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<td>Operation</td>
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<td>Adjuvant CT</td>
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<td>Adjuvant RT</td>
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<td>Interval between RT and Docetaxel</td>
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<tr>
<td>Recall phenomenon</td>
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<tr>
<td>First sign of Radiation</td>
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<td>Recovery</td>
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<td>Delay in CT</td>
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Patients number 1 and 2 were referred to medical oncology and radiation oncology departments after modified radical mastectomy and considered to be high risk for local and systemic relapse. Patient number 3 was treated surgically for an axillary lesion reported to be malignant melanoma 16 months earlier, but retrospectively diagnosed as axillary involvement of breast cancer, after appearance of the primary in the breast. After mastectomy and re-exploration of the axilla, this patient was also treated with same protocol. Patients 1 and 3 were treated first with AC (Cyclophosphamide 600 mg/m², adriamycin 60 mg/m²) and patient 2 with CEF (cyclophosphamide 500 mg/m², epirubicin 75mg/m², 5-fluourouracil 500mg/m²). Treatment cycles were repeated every three weeks if complete hematological recovery had occurred. Radiotherapy was delivered at least 1 week after the last cycle of initial chemotherapy, with linear accelerator or/and Co 60 teletherapy machine, including supraclavicular, axillary and internal mammary lymph nodes and chest wall. In patient number 2,
radiotherapy was stopped early because an axillary node on the other side appeared, upstaging the patient to stage 4.

Four to 5 days after the first cycle of docetaxel all three patients developed a localized painful erythema and oedema in the skin over the previous site of radiation therapy, clearly limited with irradiated area. Lesions improved with hyperpigmentation in one to three weeks with local treatment only. This reaction caused 5 days of delay in the second cycle in one of the patients but planned 4 cycles could be administered without any other problem in all of them.

**Discussion**

The term "radiation recall" is used to define a reaction, produced by a chemotherapeutic agent in a previously irradiated field, without occurring in nonirradiated sites. Enhancement of radiation injury to the skin and mucous membranes has been observed with a number of chemotherapeutic agents within various periods after radiotherapy. This phenomenon has been known for decades. Although, actinomycin-D and doxorubicin are commonly associated drugs, alkylating agents, bleomycin, vinblastine, edatrexate, VP-16 and tamoxifen were also reported to cause this phenomenon (4-7). More recently, the mitotic inhibitors paclitaxel and docetaxel have been reported to induce radiation recall (8-13). Paclitaxel and docetaxel are known to potentiate the effect of radiotherapy. They block cells in G2-M thus increasing the proportion of tumor cells with increased sensitivity to ionizing radiotherapy and also possibly by reoxygenation of hypoxic tumor cells, render these cells sensitive to radiation (15-17).

The mechanism of radiation recall is poorly understood. Skin, lung and mucous membranes are the most commonly reported tissues, effected from recall, and this makes reasonable to assume that the principle defect is due to the radiation and cytotoxic chemotherapy discloses the subclinical injury. The proposed theory, concerning lethal mutations among the progeny of a surviving cell as the basis for the recall effect, was unproved (18). Case reports with drugs other than cytotoxics and photo recall phenomenon described with antibiotics increases the confusion about the mechanism (19-20). Radiation recall occurring in patients with significant immunosuppression makes it unlikely that the phenomenon is a lymphocyte-mediated reaction (21,22).

The interval between the radiation and chemotherapy changes from weeks to years in reported cases (4-13,23-25). If interval is important, short interval between docetaxel and radiotherapy in our cohort, may be the reason for the high incidence. However, in an experimental study with mice, the interaction between irradiation and adriamycin was more pronounced when the interval between the two modalities was long (26). At the present, it is still unknown if the interval clinically effect the incidence of this phenomenon and if different mechanisms play role in early and late radiation recall.

Postmastectomy radiation is a long history of debate. There is still controversy if it is needed and what should be the optimal sequencing of two modality. Last two positive adjuvant radiotherapy studies, opened a new area of the discussion although criticized a lot (1-2). However, at present, most of the patients with either primary tumor size more than 5 cm or with more than 3
positive axillary nodes or pectoral fascial involvement, are widely treated with postmastectomy radiation. Several series have found an increased incidence of locoregional recurrence in patients who received radiation following completion of chemotherapy (27-28). In a randomized trial reported by Lara et al (29), three cycles of CMF followed by radiotherapy and another three cycles was significantly better from either six cycles of CMF first or radiotherapy first. This so called "sandwich approach" is widely used. Our patients received radiotherapy after initial anthracyclin based regimen with a sandwich approach followed by docetaxel. Although anecdotal, frequent radiation recall with this approach should be concerned as an important observation and kept in mind.

References
3. Henderson IC, Berry D, Demetri G, et al. Improved disease free survival (DFS) and overall survival (OS) from the addition of sequential paclitaxel (T) but not from the escalation of doxorubicin (A) dose level in the adjuvant chemotherapy of patients with node positive primary breast cancer. Proc Am Soc Clin Oncol 1998;17:101a. Abstract 390A.