Original Article

# Evaluation of the Effect of Radiotherapy Timing on Toxicity in HER2-Positive Breast Cancer Receiving Trastuzumab Emtansine in the Adjuvant Period

# Adjuvan Dönemde Trastuzumab Emtansin Alan HER2 Pozitif Meme Kanserinde Radyoterapi Zamanlamasının Toksisiteye Etkisinin Değerlendirmesi

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**ABSTRACT**

**Introduction:** Breast cancer is the second leading cause of cancer-related deaths in women.Approximately 20-25% of breast cancers have HER2 overexpression and are associated with poor prognosis.With the use of HER2-targeted therapies, there has been an increase in treatment success in breast cancer with HER2 overexpression.
Trastuzumab emtansine (T-DM1) is the antibody-drug conjugate of trastuzumab and the cytotoxic agent emtansine (DM1), a maytansine derivative and microtubule inhibitor.
The aim of our study is to evaluate the effect of continuing T-DM1 on toxicity in patients receiving adjuvant radiotherapy with real-life data. There is no study in the literature yet that evaluates the toxicity of adjuvant T-DM1 in real life.
**Materials and Methods:** The patients' files were examined retrospectively. The primary endpoint of the study was determined as whether the timing of radiotherapy increased adjuvant T-DM1 toxicity. The patients were divided into two groups: those who continued T-DM1 during adjuvant radiotherapy and those who started after T-DM1 adjuvant radiotherapy
**Results:** A total of fifty patients were included in the study. While twenty (40%) of the patients received sequential radiotherapy with T-DM1, thirty (60%) continued T-DM1 during radiotherapy.No significant difference was detected in terms of toxicity in both groups
**Conclusion:** In our study, we saw that some physicians started T-DM1 after radiotherapy, thinking that toxicity might increase. However, we saw in the analysis that there is no significant increase in toxicities with simultaneous use. We think that as the use of antibody-drug conjugates in the clinic increases, more studies will be needed to determine the timing of radiotherapy

**Keywords:** Antibody-drug conjugates, Adjuvant T-DM1, Trastuzumab emtansine, HER2-positive breast cancer

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## ÖZET

**Amaç:** Meme kanseri kadınlarda kanser ilişkili ölümlerde ikinci sırada gelmektedir. Meme kanserinin yaklaşık %20-25 inde HER2 overeksperyonu olup, kötü prognozla ilişkilidir. HER2 hedefli tedavilerin kullanımı ile HER2 overekspresyonu görülen meme kanserinde tedavi başarısında artış görülmüştür.
Trastuzumab emtansin (T-DM1), trastuzumab ile bir maytansin türevi ve mikrotübül inhibitörü olan sitotoksik ajan emtansinin (DM1) antikor-ilaç konjugatıdır.
Çalışmamızın amacı adjuvan radyoterapi alan hastalarda T-DM1 e devam etmenin toksisite üzerine etkisini gerçek yaşam verileri ile değerlendirmektir. Literatürde adjuvan T-DM1 in toksistesini gerçek yaşamda değerlendiren çalışma henüz bulunmamaktadır.
**Gereç ve Yöntemler:** Hastaların dosyaları geriye dönük olarak incelendi. Çalışmanın birincil son noktası, radyoterapi zamanlamasının adjuvan T-DM1 toksisitesi üzerine etkisi olarak belirlendi. Hastalar adjuvan radyoterapi sırasında T-DM1'e devam edenler ve T-DM1 adjuvan radyoterapiden sonra başlayanlar olmak üzere iki gruba ayrıldı.
**Bulgular:** Çalışmaya totalde elli hasta dahil edildi. Hastaların yirmisi(%40) T-DM1 ile radyoterapiyi sekansiyel almışken, otuzu(%60) radyoterapi süresince T-DM1 e devam etmişti.Her iki grupta toksisite açısından anlamlı fark saptanmadı.
**Sonuç:** Çalışmamızda hekimlerin bir kısmının toksisite artabilir düşüncesiyle radyoterapi sonrası T-DM1 başladığını gördük. Fakat analizde gördük ki eş zamanlı kullanımında toksisitelerde anlamlı artış olmamaktadır.Antikor-ilaç konjugatlarının klinikte kullanımı arttıkça radyoterapi ile zamanlamasının belirlenmesi için daha çok çalışmaya ihtiyaç olacağını düşünmekteyiz

**Anahtar Kelimeler:** Antikor-ilaç kojugatları, Adjuvan T-DM1, Trastuzumab emtansin, HER2 pozitif meme kanseri

## Introduction

Breast cancer is the second leading cause of cancer-related deaths among women.[1] Approximately 20-25% of breast cancers have HER2 overexpression and are associated with poor prognosis.[2] With the use of HER2-targeted therapies, there has been an increase in treatment success in breast cancer with HER2 overexpression.In the Phase-II NeoSphere study, pertuzumab was added to trastuzumab and docetaxel in localized or locally advanced HER2 overexpressing breast cancer patients, and a significant increase in pathological complete response rates was observed (29% vs. 46%). The increase in pathological response rates is associated with improved survival.[3]

Trastuzumab emtansine (T-DM1) is the antibody-drug conjugate of trastuzumab and the cytotoxic agent emtansine (DM1), a maytansine derivative and microtubule inhibitor. T-DM1 maintains trastuzumab activity while ensuring the intracellular delivery of DM1 to cells overexpressing HER2.[4] In the Katherine study, the use of T-DM1 and trastuzumab in the adjuvant period were compared in patients who received neoadjuvant treatment and had residual disease in the breast or axillary lymph node. 1486 patients were included in the study and randomized, 743 in the T-DM1 group and 743 in the trastuzumab group. Invasive disease or death occurred in 91 patients (12.2%) in the T-DM1 group and 165 patients (22.2%) in the trastuzumab group. Invasive disease-free survival was significantly higher in the T-DM1 group compared to the trastuzumab group (HR for invasive disease or death, 0.50; 95% confidence interval, 0.39 to 0.64; P<0.001). In this study, T-DM1 was continued during the adjuvant period during adjuvant radiotherapy. No significant increase in toxicities was observed in this study.[5]

In clinical practice, radiotherapy and chemotherapy applications in the adjuvant period are applied sequentially in breast cancer, as in most cancers. Concurrent application suggests to the clinician that toxicity may increase. Some clinicians wait for the end of radiotherapy to start T-DM1 in the adjuvant period.The aim of our study is to

 

evaluate the effect of continuing T-DM1 on toxicity in patients receiving adjuvant radiotherapy with real-life data. There is no study in the literature yet that evaluates the toxicity of adjuvant T-DM1 in real life.

## Materials and Methods

Fifty breast cancer patients with Her-2 overexpression, over the age of 18, who received adjuvant T-DM1 after receiving neoadjuvant treatment between 2021 and 2023, were included in the study. The study was conducted in a multicenter manner. Patients who had a pathological complete response to neoadjuvant treatment and did not receive T-DM1 in the adjuvant period were excluded from the study.

Approval was received from the Non-Invasive Clinical Research Ethics Committee of our hospital.The patients' files were examined retrospectively. Demographic data such as age, gender, menopause status, family history of breast cancer, and the patient's clinical stage at the time of diagnosis, treatment received in the neoadjuvant period, and pathological stage were recorded. Toxicities that developed while receiving adjuvant T-DM1 were examined.Toxicities were evaluated and graded according to CTCAE version 5. All Grade I-IV toxicities were considered significant and noted. The primary endpoint of this study was to determine whether the timing of radiotherapy increased adjuvant T-DM1 toxicity. The patients were divided into two groups: those who continued T-DM1 during adjuvant radiotherapy and those who started using T-DM1 after adjuvant radiotherapy. Statistical Analysis

In the descriptive statistics of the research, continuous variables are mean (standard deviation), median (range); Categorical variables were presented as frequency (percentage). Chi-square or Fisher's Exact test was used to compare categorical variables of two independent groups. Independent sample t-test was used for comparison of parametric data, and Mann-Whitney-U test was used for comparison of non-parametric data.

## Results

A total of fifty patients were included in the study. While twenty (40%) of the patients received sequential radiotherapy with T-DM1, thirty (60%) continued T-DM1 during radiotherapy. Twenty-seven (54%) of the patients were premenopausal, while twenty-three (46%) were peri-postmenopausal. Forty-five patients (90%) were node-positive at diagnosis. (The demographic characteristics of the patients are shown in Table-1). Of the patients who received sequential radiotherapy with T-DM1 in the adjuvant period, one (5%) had neutropenia, seven (35%) had thrombo-cytopenia, one (5%) had anemia, two (10%) had hepatotoxicity. A decrease in ejection fraction was observed in one (5%) of them. All of these toxicities were at grade 1-2 level. Radiodermatitis was observed in five (25%) patients and one (5%) was grade 3 and four (20%) was grade 1-2.

In patients who continued T-DM1 during adjuvant radiotherapy, two (6.6%) had neutropenia, three (10%) had thrombo-cytopenia, two(6.6%) had anemia, and two (6.6%) had hepatotoxicity. All of these toxicities were at grade 1-2 level. Neuropathy was observed in one patient and since it was at grade 3 level, treatment was discontinued and trastuzumab was continued. In one patient, treatment was discontinued because pneumonitis was observed at the radiotherapy site and trastuzumab was continued. Radiodermatitis was observed in five (16%) patients and three (10%) of them were at grade 3 level (shown in Table-2).

## Discussion

In our study, we planned to evaluate the effect of the timing of radiotherapy on toxicities in her-2 positive breast cancer patients receiving T-DM1 in the adjuvant period. In the Katherine study,

 

Table-1: Demographic Characteristics of Patients

| | Sequenced Radiotherapy(n:20) | Concurrent Radiotherapy(n:30) | p-value | All patients |
|---|---|---|---|---|
| Age(mean) | 50,6 | 49,3 | | 49,8 |
| Menopause | | | | |
| Premenopausal | 10(50) | 17(57) | 0,643 | 27 |
| Peri-postmenopausal | 10 (50) | 13(43) | | 23 |
| Familial breast cancer | | | | |
| No | 14(70) | 23(76.7) | 0,599 | 37 |
| Yes | 6(30) | 7(23.3) | | 13 |
| Clinical T stage | | | | |
| T1 | 2(10) | 2(6,7) | 0,744 | 4 |
| T2 | 14(70) | 23(76,7) | | 37 |
| T3-T4 | 4(20) | 5(16,6) | | 9 |
| Clinical nodal status | | | | |
| Node positive | 19(5) | 26(86,6) | 0,024 | 45 |
| Node negative | 1(95) | 4(13,3) | | 5 |
| ER status | | | | |
| Positive | 14(70) | 19(63,3) | 0,626 | 33 |
| Negative | 6(30) | 11(367) | | 17 |
| PR status | | | | |
| Positive | 13(65) | 17(56,7) | 0,556 | 30 |
| Negative | 7(35) | 13(43,3) | | 20 |
| Grade | | | | |
| Grade 1-2 | 7(35) | 12(41,3) | 0,672 | 19 |
| Grade 3 | 13(65) | 17(58,6) | | 30 |
| pT stage | | | | |
| T0-1-2 | 18(90) | 26(90) | 0,406 | 44 |
| T3-4 | 2(10) | 3(10) | | 5 |
| pN stage | | | | |
| N0-1 | 16(80) | 24(82,7) | 0,616 | 40 |
| N2-3 | 4(20) | 5(17,2) | | 9 |

ER: Estrogen receptor PR:Progesterone receptor

Table-2:Trastuzumab Emtansine Related Toxicities

| | Sequenced RT | | Concurrent RT | | p-value |
|---|---|---|---|---|---|
| | var | yok | var | yok | |
| Neutropenia | 1(5) | 19(95) | 2(6,6) | 28(93,3) | 0,657 |
| Thrombocytopenia | 7(35) | 13(65) | 3(10) | 27(90) | 0,027 |
| Anemia | 1(5) | 19(95) | 2(6,6) | 28(93,3) | 0,657 |
| Hepatotoxicity | 2(10) | 12(90) | 2(6,6) | 28(93,3) | 0,521 |
| Decrease in ejection fraction | 1(5) | 18(95) | 0(0) | 30(100) | 0,388 |
| Neuropathy | 0(0) | 20(100) | 1(3,3) | 29(96,7) | 0,600 |
| Pneumonitis | 0(0) | 20(100) | 1(3,3) | 29(96,7) | 0,600 |
| Radiodermatitis | 5(25) | 15(75) | 5(16) | 25(84) | 0,390 |
| All toxicities | 9(45) | 11(55) | 12(40) | 18(60) | 0,556 |

patients who received T-DM1 in the adjuvant period also received radiotherapy simultaneously.[5] When we look at the whole study, there was no significant increase in toxicities compared to the use of T-DM1 in the metastatic period. Of course, this result may be due to the better performance and better drug tolerance of patients in the early stages. In most cancers, chemotherapy and radiotherapy are not used simultaneously in the adjuvant period due to the expectation that toxicity may increase. For example, in lung cancer, postoperative radiotherapy is recommended in cases of positive surgical margins or N2 disease, but it is recommended that its timing be planned after chemotherapy.[6] Antibody-drug conjugates have become widely used in clinical practice in recent years.These drugs, which are primarily used in the metastatic stage, were indicated for use in the early stage, as the use of T-DM1 in the adjuvant period showed progression-free survival. We think that in the future, as the use of antibody-drug conjugates increases and new indications develop, the timing of radiotherapy in the adjuvant period will be discussed more frequently. In our study, we saw that some physicians started T-DM1 after radiotherapy, thinking that toxicity might increase. However, we saw in the analysis that there is no significant increase in toxicities with concurrent use. Although there was no statistically significant increase in toxicities, pneumonitis was observed in the radiotherapy field in one of the patients receiving concurrent therapy, leading to discontinuation of treatment, and neuropathy was observed in one patient, which could lead to discontinuation of treatment. This supports the reservations about concurrent use. The main limitations of our study were its retrospective nature and small number of patients. As the number of patients increases, the increase in concurrent use may reach statistically significant levels.

As a result, we think that as the use of antibody-drug conjugates in the clinic increases, more studies will be needed to determine the timing of radiotherapy

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