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

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ABSTRACT

Aim: Breast cancer is the second leading cause of cancer-related deaths in women. Approximately 20-25% of breast cancers express HER2 and are associated with poor prognosis. With the use of HER2-targeted therapies, there has been an increase in treatment success for breast cancer cells overexpressing HER2. Trastuzumab extensive (T-DM1) is the antibody-drug conjugate of trastuzumab and the cytotoxic agent extensive (DM1), a maytansine derivative and microtubule inhibitor. The aim of our study was to evaluate the effect of continuing T-DM1 therapy on toxicity in patients receiving adjuvant radiotherapy using real-world data. There is no study in the literature that evaluates the toxicity of adjuvant T-DM1 in real life.

Methods: Patient files were examined retrospectively. The primary endpoint of the study was whether the timing of radiotherapy increased adjuvant T-DM1 toxicity. Patients were divided into two groups: those who continued T-DM1 during and after T-DM1 adjuvant radiotherapy.

Results: A total of 50 patients were included in the study. 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 observed that some physicians started T-DM1 after radiotherapy considering that toxicity might increase. However, we observed in the analysis that there was no significant increase in the toxicities with simultaneous use. We believe that as the use of antibody-drug conjugates in the clinic increases, more studies are needed to determine the timing of radiotherapy.

Keywords: Antibody-drug conjugates, adjuvant T-DM1, trastuzumab extensive, HER2-positive breast cancer

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 for breast cancer cells overexpressing HER2. In the phase II NeoSphere study, pertuzumab was added to trastuzumab and docetaxel in patients with localized or locally advanced HER2-overexpressing breast cancer, and a significant increase in pathological complete response rates was observed (29% vs. 46%). An increase in pathological response rates is associated with improved survival [3].

Trastuzumab extensive (T-DM1) is the antibody-drug conjugate of trastuzumab and the cytotoxic agent extensive (DM1), a maytansine derivative and microtubule inhibitor. T-DM1 maintains trastuzumab activity while ensuring intracellular delivery of DM1 to cells overexpressing HER2 [4]. In the

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Katherine study, the use of T-DM1 and trastuzumab in the adjuvant period was compared among patients who received neoadjuvant treatment and had residual disease in the breast or axillary lymph node. A total of 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%) patients in the trastuzumab group. Invasive disease-free survival was significantly higher in the T-DM1 group than in the trastuzumab group (HR, 0.50; 95% confidence interval, 0.39 to 0.64; p<0.001). T-DM1 was continued during the adjuvant period of adjuvant radiotherapy. No significant increase in toxicity was observed in this study [5].

In clinical practice, radiotherapy and chemotherapy in the adjuvant period are sequentially applied to breast cancer, as in most cancers. Concurrent application suggests that toxicity may increase. Some clinicians wait until the end of radiotherapy to start T-DM1 in the adjuvant period. The aim of our study was to evaluate the effect of continuing T-DM1 therapy on toxicity in patients receiving adjuvant radiotherapy using real world data. There are no studies in the literature that evaluate the toxicity of adjuvant T-DM1 in the real world.

Methods

Fifty breast cancer patients with HER2 overexpression, aged >18 years, 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 setting. Patients who had a pathological complete response to neoadjuvant therapy but did not receive T-DM1 during the adjuvant period were excluded from the study.

Approval was received from the Non-Invasive Clinical Research Ethics Committee of University of Health Sciences Türkiye, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (decision number: 2023-11/91, date: 16.11.2023). The patient files were examined retrospectively. Demographic data, such as age, sex, menopausal status, family history of breast cancer, clinical stage at the time of diagnosis, treatment received during 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 1-4 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. Patients were divided into two groups: those who continued T-DM1 during and those who started using T-DM1 after adjuvant radiotherapy.

Statistical Analysis

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

Results

A total of 50 patients were included in the study. Twenty (40%) of the patients received sequential radiotherapy with T-DM1, thirty (60%) continued T-DM1 during radiotherapy. Twenty-seven (54%) patients were premenopausal, while 23 (46%) were peri-postmenopausal. Forty-five patients (90%) were node-positive upon 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 thrombocytopenia, one (5%) had anemia, and 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, with one (5%) having grade 3 and four (20%) was grade 1-2.

In patients who continued T-DM1 during adjuvant radiotherapy, two (6.6%) developed neutropenia, three (10%) developed thrombocytopenia, two (6.6%) developed anemia, and two (6.6%) developed hepatotoxicity. All of these toxicities were at grade 1-2 level. Neuropathy was observed in one patient, and because it was at grade 3, 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 aimed to evaluate the effect of the timing of radiotherapy on toxicities in patients with HER2 positive breast cancer who received T-DM1 in the adjuvant period. In the Katherine study, patients who received T-DM1 in the adjuvant period also received radiotherapy simultaneously [5]. When we looked at the entire study, there was no significant increase in toxicities compared with the use of T-DM1 during 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 during the adjuvant period because of the potential increase in toxicity. For example, in lung cancer, postoperative radiotherapy is recommended in cases with positive surgical margins or N2 disease, but it is recommended that the timing of radiotherapy 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 because the use of T-DM1 in the adjuvant period resulted in progression-free survival. We believe that in the future, as the use of antibody-drug conjugates increases and new indications develop, the

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 stage T				
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
	Yes	No	Yes	No	
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

timing of radiotherapy in the adjuvant period should be more frequently discussed. In our study, we observed that some physicians started T-DM1 after radiotherapy considering that toxicity might increase. However, we observed in the analysis that there was 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 treatment discontinuation, and neuropathy was observed in one patient, which could lead to treatment discontinuation. This supports reservations about concurrent use.

Study Limitations

The main limitations of our study were its retrospective nature and small number of patients. The increase in concurrent use may reach statistically significant levels as the number of patients increases.

Conclusion

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

Ethics

Ethics Committee Approval: Approval was received from the Non-Invasive Clinical Research Ethics Committee of University of Health Sciences Türkiye, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (decision number: 2023-11/91, date: 16.11.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: İ.D.O., Concept: İ.D.O., Design: İ.D.O., C.K., Ö.A., Data Collection or Processing: O.K., G.K., Ö.F.K., T.B., Analysis or Interpretation: İ.D.O., C.K., Literature Search: İ.D.O., Writing: İ.D.O., C.K.

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