Evaluation of Demographic Parameters, Disease Burden, and Cardiovascular Risk Factors in Patients Who Received Primary Prophylaxis with Dexrazoxane for Prevention of Anthracycline-Induced Cardiotoxicity

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ABSTRACT Objective: This retrospective study aimed to reveal the demographic parameters, disease burden, and cardiovascular risk factors in patients who received primary prophylaxis with dexrazoxane for the prevention of anthracycline-induced cardiotoxicity. We also evaluated the compliance of dexrazoxane use as per the American Society of Clinical Oncology (ASCO) Clinical Practice Guideline (CPG) criteria in these patients. **Material and Methods:** Data of 44 patients were retrospectively analyzed. A data registration form comprising 31 questions, including demographic characteristics, anthracycline treatment and dosage, chemotherapeutic agents, radiotherapy, surgical procedures, and data on cardiac functions and cardiovascular risk parameters, were retrospectively analyzed for each patient included in the study. **Results:** The average age of patients was 53 years, and the percentage of female patients was 88.6%, among which, the primary diagnosis was breast cancer. In 32 of 44 patients, no oncological treatment was administered before the anthracycline treatment. In all 44 patients, the ejection fraction value before anthracycline treatment was 60% or higher. Eleven patients received cumulative high-dose anthracycline treatment (doxorubicin $\geq$250 mg/m^2, epirubicin $\geq$600 mg/m^2). As per the recommendations of the ASCO CPG, 77.2% of patients in the study population were at high risk for the development of cardiac dysfunction. For 22.8% of the patients, the guideline recommendation for the development of cardiac dysfunction did not exist. Six of these ten patients, which are not considered to be at high risk for developing cardiac dysfunction, had at least one of the cardiovascular risk factors: smoking, hypertension, diabetes, dyslipidemia, or obesity. **Conclusion:** Cardiotoxicity of anthracyclines is dose-dependent and can occur at any time in the treatment course with acute, subacute, and late-onset presentations. Cardiotoxicity of anthracyclines is one of its most serious adverse effects though occasionally, precluding its usage even in potentially curative cases. Co-administration of dexrazoxane has been shown to reduce cardiotoxicity effectively. Further studies on the use of dexrazoxane in patients who are not in the high-risk group for anthracycline-induced cardiotoxicity are warranted.

Keywords: Anthracyclines; cancer; cardiac dysfunction; cardiotoxicity; dexrazoxane; prevention

Despite advancements in oncological treatments, anthracyclines still form the basis of the treatment. Anthracycline chemotherapy plays a prominent role in treating many forms of cancer. Unfortunately, the dose-dependent and cumulative cardiotoxicity limit the use of anthracyclines.[1] Cardiotoxic side effects limit their dosing, and improved cancer outcomes expose the cancer survivor to increased cardiovascular morbidity and mortality. The exact mechanism of anthracycline-induced cardiotoxicity is still unclear, although it is likely to be multifactorial. The primary mechanism of cardiotoxicity may involve direct pathways for reactive oxygen species generation and topoisomerase II, and other indirect pathways. Application of various strategies can minimize anthracycline-induced cardiotoxicity; one such method is dexrazoxane, a cardioprotective agent. Dexrazoxane has been used in cancer patients to prevent anthracycline-related cardiotoxicity since the 1980s. Dexrazoxane, an ethylene diamine tetraacetic acid, such as

bisdioxopiperazine, becomes hydrolyzed within the cardiomyocyte to form a potent chelator of heavy metals, especially iron.[2] Cancer outcomes continue to improve due to early detection and newer targeted therapies, with anthracycline chemotherapy playing a significant role in the modern era of cancer treatment. Fifty years since its discovery, anthracycline antitumor, and cardiotoxic mechanisms continue to evoke considerable interest in basic science and clinical trial research.[3]

Anthracyclines belong to the class of antitumor drugs and are widely used to treat several malignancies such as leukemia, lymphoma, sarcoma, and carcinoma.[4] Currently, anthracycline agents such as doxorubicin, idarubicin, and epirubicin are widely recommended to treat malignances like hematological malignancies, soft tissue sarcomas, and solid tumors in both children and adults.[5] However, the dose-dependent and cumulative cardiotoxicity associated with anthracycline significantly limit the use of these agents.[6] Anthracycline-induced cardiotoxicity presents as dilated cardiomyopathy, with or without symptoms of heart failure.[7] As a result, anthracycline-induced cardiotoxicity can be classified as acute/subacute or chronic/late cardiotoxicity. This clinical picture appears to be a devastating side effect leading to adverse events like morbidity, impairment in quality of life, and premature death.[8-10]

In oncology clinics in Turkey, there is a need for a clinical study in which the demographic characteristics, disease burden data, and cardiovascular risk factors of the cancer patients treated with cardioprotective dexrazoxane to minimize anthracycline-induced toxicity are evaluated. Besides, real-world data of this patient profile should be presented, and the use of dexrazoxane in our country should be considered in line with American Society of Clinical Oncology (ASCO) Clinical Practice Guideline (CPG). According to the recommendations of ASCO CPG, clinicians may incorporate several strategies, including the use of the cardioprotectant dexrazoxane, to prevent cardiotoxicity in patients planning to receive high-dose anthracyclines (e.g., doxorubicin $\geq$250 mg/m^2, epirubicin $\geq$600 mg/m^2).[11] Based on this need, the authors conducted this study in which the data of 44 patients who visited the oncology clinics of two

different hospitals in our country were retrospectively analyzed.

MATERIAL AND METHODS

The data of 44 patients admitted between January 1, 2019, and December 31, 2019, in the oncology clinics of İstanbul Şişli Etfal Training and Research Hospital and Antalya Memorial Hospital based in Turkey were retrospectively analyzed. The patients included in the study had a history of anthracycline treatment for various malignancies and received primary prophylaxis with dexrazoxane before anthracycline treatment. Based on patient files and hospital records, a data registration form comprising 31 questions, including demographic characteristics of the patients, anthracycline treatment and dosage, chemotherapeutic agents other than anthracycline, other oncological therapies such as radiotherapy and surgical procedures, and information on cardiac functions and cardiovascular risk parameters were retrospectively filled in for each study participant. The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethics committee approval was taken from Health Sciences University Şişli Hamidiye Etfal Training and Research Hospital (issue number: 2881, dated: 07/07/2020).

RESULTS

Forty-four patients were included in this retrospective study. The average age of the patients was 53 years, the average height was 161.2 cm, the average body weight was 74.7 kg, and the average body mass index (BMI) was 28.8 (Table 1). The percentage of female patients was 88.6% (39/44), and 29.5% of all patients were 60 years old and above (13/44). The primary diagnosis in 39 of 44 (88.6%) patients was breast cancer. Other primary diagnoses were sarcoma (2), lung cancer (1), thyroid cancer (1), and nasopharyngeal cancer (1) (Table 1). In 28 of 39 (71.8%) patients with a primary breast cancer diagnosis, the disease was at a locally advanced stage, and 11 patients (28.2%) had metastatic disease.

In 32 of 44 (72.7%) patients, no oncological treatment was administered before anthracycline treatment. Nineteen of 44 (43.1%) patients had a his-

tory of oncological surgery before anthracycline chemotherapy. Examination of other chemotherapeutic agents used in conjunction with anthracycline treatment or sequence were examined, cyclophosphamide was found to be used in 33 of 44 (75%) patients. Eight of 44 patients (18.1%) had a history of previous anthracycline treatment, and in four of these patients, the cumulative dose was 240 mg/m^2 and higher. Radiotherapy (even in the heart area) was planned in 12 of 44 patients (27.2%). In all 44 patients, the ejection fraction (EF) value before anthracycline treatment was 60% and higher. After anthracycline treatment, data on the EF value were available in 4 patients, and all had an EF value of 60% and higher. During anthracycline therapy, febrile neutropenia occurred in only one patient (2.2%). In 40 of 44 (90.9%) patients, G-CSF was used before anthracycline treatment.

In 11 of 44 patients (25%), high-dose anthracycline therapy was used according to the anthracycline dose specified in the ASCO CPG (doxorubicin ≥250 mg/m^2, epirubicin ≥600 mg/m^2 (Table 2). Cardiovascular risk factors in patients were reported as: 47.7% (21/44) of patients had a history of smoking, 38.6% (17/44) had hypertension, 25% (11/44) had diabetes, 2.2% (1/44) had dyslipidemia, and 43.1% of patients had obesity (19/44) (Table 2). The proportion of patients with at least one of these cardiovascular risk factors listed above was 81.8%, that with two or more risk factors was 40.9%, and that with at least three risk factors was 25%. Two patients (4.5%) had a history of myocardial infarction, and no patient had a history of moderate to severe heart disease (Table 1).

In 39 of 44 (88.6%) patients, the primary diagnosis was breast cancer. The demographics of this patient subgroup were as follows: the average age of breast cancer patients was 51.6, and 23% (9/39) of the patients were 60 years of age and above. The average body weight of breast cancer patients was 74.9 kg, and the average BMI was 29.2. In 28 of 39 (71.7%) patients with breast cancer as the primary di-

TABLE 1: Demographic characteristics, disease burden, treatment highlights, and cardiovascular risk parameters of patients.		
Parameter	Total population (n=44)	Primary diagnosis of breast cancer (n=39)
Mean age (range)-y	53 (28-78)	51.6 (28-78)
Age ≥60-n, (%)	13 (29.5)	9 (23)
Female-(%)	39 (88.6)	38 (97.4)
Male-(%)	5 (11.4)	1 (2.6)
Mean height-cm	161.2	160.4
Mean weight-kg	74.7	74.9
Mean BMI	28.8	29.2
Oncological treatment prior to anthracycline-n, (%)	12 (27.2)	10 (25.6)
History of surgery before medical therapy-n, (%)	19 (43.1)	17 (43.5)
RT where the heart is in the treatment field-n, (%)	12 (27.2)	10 (25.6)
High-dose anthracycline-n, (%)	11 (25.0)	10 (25.6)
Cardiovascular risk factors		
Smoking history-n, (%)	21 (47.7)	19 (48.7)
Hypertension-n, (%)	17 (38.6)	13 (33.3)
Diabetes-n, (%)	11 (25.0)	8 (20.5)
Dyslipidemia-n, (%)	1 (2.2)	1 (2.5)
Obesity-n, (%)	19 (43.1)	18 (46.1)
No CV risk factor	8 (18.2)	8 (20.5)
≥1 CV risk factor	36 (81.8)	31 (79.4)
≥2 CV risk factor	18 (40.9)	15 (38.4)
≥3 CV risk factor	11 (25.0)	9 (23.0)

BMI: Body mass index; RT: Radiotherapy; CV: Cardiovascular.

agnosis, the disease was at a locally advanced stage, and 11 patients (28.3%) had metastatic disease. In 18 of 39 (46.1%) patients whose primary diagnosis was breast cancer, the tumor was located on the left side; in 4 patients (10.2%), the tumor was bilateral, and 25.6% (10/39) of the patients had HER-2 receptor positivity. As per the treatment doses stated in ASCO CPG, 10 of 39 (25.6%) breast cancer patients had a history of high-dose anthracycline treatment (doxorubicin ≥250 mg/m², epirubicin ≥600 mg/m²). Cardiovascular risk factors in breast cancer patients were found to be as follows: 48.7% of the patients had a smoking history, 33.3% had hypertension, 20.5% had diabetes, 2.5% had dyslipidemia, and 46.1% had obesity (Table 2). The rate of breast cancer patients with at least one cardiovascular risk factor was 79.4%, that patients with at least two risk factors were 38.4%, and the rate of patients with at least three risk factors was 23%.

DISCUSSION

The ASCO published a CPG in 2017 to develop recommendations for the prevention and monitoring of cardiac dysfunction in survivors of adult-onset cancers.[11] This retrospective study evaluated the risk situations for the development of cardiac dysfunction within the scope of ASCO CPG. According to the evaluation, 77.2% (34/44) of the patients are considered to be at high risk for developing cardiac dysfunction as per the guideline recommendations (Table 2). For 22.8% (10/44) of the patients, there was no guideline recommendation regarding the development of cardiac dysfunction. Six (60%) of these ten patients, not considered to be at high risk for developing cardiac dysfunction, had at least one cardiovascular risk factor (smoking, hypertension, diabetes, dyslipidemia, or obesity).

In the subgroup of 39 patients with the primary diagnosis of breast cancer, the proportion of patients considered to be at high risk for developing cardiac dysfunction according to the guideline recommendations was 74.3% (29/39) (Table 2). There is no guideline recommendation for the remaining 25.7% (10/39) of the patients in terms of the development of cardiac dysfunction. Six (60%) of these ten patients not considered to be high risk for developing cardiac dysfunction had at least one of the cardiovascular risk factors (smoking, hypertension, diabetes, dyslipidemia, or obesity). Although 10 of 44 (22.8%) patients in this study were not in the high-

TABLE 2: Primary diagnoses of the study population, the number of patients receiving high-dose anthracycline, percentages of cardiovascular risk factors, and percentages of patients at high risk for developing cardiac dysfunction in the study population and the breast cancer subgroup.		
Parameter	**Total population (n=44)**	
Primary diagnosis, n		
Breast cancer	39	
Sarcoma	2	
Lung cancer	1	
Thyroid cancer	1	
Nasopharyngeal cancer	1	
Parameter	**Total population (n=44)**	**Primary diagnosis of breast cancer (n=39)**
Patients receiving high-dose anthracycline, n	11	10
Cardiovascular risk factors, %		
Smoking history	47.7	48.7
Hypertension	38.6	33.3
Diabetes	25	20.5
Dyslipidemia	2.2	2.5
Obesity	43.1	46.1
Proportion of patients at high risk of developing cardiac dysfunction, %	77.2	74.3

risk patient group for developing cardiac dysfunction according to the ASCO CPG, dexrazoxane was used as the primary prophylaxis in these patients. In addition, 60% of the patients in the study who were not in the high-risk group for cardiac dysfunction had at least one of the cardiac risk factors. These considerations may constitute a justification for the use of dexrazoxane in the group of patients who received low-dose anthracycline treatment and were not in the high-risk group. However, more studies with long-term follow-up are needed to justify the fact.

Anthracyclines are the drugs of first choice for various malignancies. Despite new developments in oncological treatment, anthracyclines still form the mainstay of the treatment. Unfortunately, the use of anthracyclines is limited by their dose-dependent and cumulative cardiotoxicity.[1] Cardiotoxicity is the primary concern as a late side effect of cancer treatment with anthracyclines. Amongst the several cancer therapies responsible for causing cardiotoxicity, anthracyclines predominantly cause myocardial dysfunction and congestive heart failure. Different approaches can minimize anthracycline-induced cardiotoxicity, one of which is the use of dexrazoxane, a cardioprotective agent. Dexrazoxane has been used in cancer patients to prevent anthracycline-related cardiotoxicity since the 1980s.[2] Long-term results in various studies prove that dexrazoxane does not reduce the effectiveness of chemotherapy in the advanced stage.[12,13] Tahover et al. showed that dexrazoxane added to adjuvant therapy did not reduce the effectiveness of chemotherapy.[14] Swain et al. established that dexrazoxane treatment combined with chemotherapy increased neutropenia.[13] Asselin et al. reported that the increase in infections with the use of dexrazoxane was not statistically significant.[12]

According to the retrospective data obtained in this study, the primary diagnosis in 88.6% of the patients was breast cancer; these patients received dose-dense anthracycline therapy, and primary prophylaxis was administered to these patients. In the present study, febrile neutropenia was observed in only one patient (2.2%), and this rate was consistent with the current literature data. However, there was no delay in chemotherapy administration, like what was noted in the study conducted by Tahover et al. It has been stated in various studies that there is no safe dose in the use of anthracycline, and cardiotoxicity may occur from the first dose.[15,16] The methods to be applied for preventing anthracycline cardiotoxicity are specified in the ASCO CPG. According to the recommendations of ASCO CPG, clinicians may incorporate several strategies, including the use of the cardioprotectant dexrazoxane, for the prevention of cardiotoxicity in patients planning to receive high-dose anthracyclines (e.g., doxorubicin $\geq$250 mg/m^2, epirubicin $\geq$600 mg/m^2). In this study, the use of dexrazoxane was carried out in accordance with the ASCO CPG in 77.2% (34/44) of the patients, and the observed side effects were consistent with the literature. For the remaining 22.8% (10/44) of the patients, no guideline recommendation for the development of cardiac dysfunction exists. Six (60%) of these ten patients had at least one of the cardiovascular risk factors (smoking history, hypertension, diabetes, dyslipidemia, or obesity). Cardiotoxicity of anthracyclines is dose-dependent and can occur at any time during the treatment course with acute, subacute, and late-onset presentations. The clinical significance of anthracycline cardiotoxicity is growing with increased cancer survivorship. Anthracyclines can also contribute to myocardial dysfunction and congestive heart failure, ultimately limiting the drug's therapeutic potential. However, recent studies prove that cardiotoxicity can also occur in this patient group. Cardiotoxicity associated with anthracycline-based chemotherapies has limited its use in patients with pre-existing cardiomyopathy or heart failure. Dexrazoxane has been used successfully to reduce cardiac toxicity in patients receiving anthracycline-based chemotherapy for cancer (predominantly women with advanced breast cancer). The drug is thought to reduce the cardiotoxic effects of anthracyclines by binding to free and bound iron, thereby reducing the formation of anthracycline-iron complexes and the subsequent generation of reactive oxygen species that are toxic to the surrounding cardiac tissue.

Murtagh et al. followed up 154 breast cancer patients, who had received adjuvant doxorubicin treat-

ment for approximately ten years and investigated the late cardiac effects of chemotherapy.[17] In most patients (83.1%), the cardiovascular risk was low, and the doxorubicin dose was 240 mg/m^2 and below in 59.7% of the patients. At the end of the 10-year follow-up period, 33.7% of patients receiving low-dose doxorubicin experienced a 0-10% decrease in left ventricular ejection fraction (LVEF) from baseline. The reduction in LVEF from baseline was 10-15% in 19.6% of patients, while a decrease in LVEF value greater than 15% from baseline was observed in 5.4% of patients. Murtagh et al. proved that breast cancer patients treated with low-dose anthracycline might also experience a loss of LVEF in the long term.[17] In addition, more than half of these patients who are not in the high-risk group for cardiac dysfunction had at least one cardiovascular risk factor. These considerations may constitute a justification for the use of dexrazoxane in this group of patients who did not fall in the high-risk group.

Finally, it can be stated that the present study comprised of a heterogeneous disease group with a small number of patients, and the patients were retrospectively examined with dexrazoxane, including the demographic characteristics and cardiovascular risk factors of the patients, regardless of the disease stage, tumor burden, and the organ from which the tumor originated. Hence, the limitations in this study can be listed as follows:

- The long-term results obtained in various studies showed that dexrazoxane does not reduce the effectiveness of chemotherapy in the advanced stage. However, in the present study, the existence of such an effect could not be evaluated due to the study design and the follow-up period.

- The sample size of the present study was not sufficient to completely reflect the data regarding the use of dexrazoxane as primary prophylaxis for the prevention of anthracycline-induced cardiotoxicity in Turkey.

The retrospective design of this study was not suitable for determining whether dexrazoxane decreases the effectiveness of chemotherapy and the role of its effectiveness in primary prophylaxis in the prevention of anthracycline-induced cardiotoxicity.

CONCLUSION

The ASCO CPG recommends the use of dexrazoxane for primary prophylaxis to prevent anthracycline-induced cardiotoxicity. In the present study, dexrazoxane was used in accordance with the ASCO CPG in 77.2% (34/44) of the patients, and the observed side effects were consistent with the literature data. For 22.8% (10/44) of the study participants, no guideline recommendation exists for the development of cardiac dysfunction. Six (60%) of these ten patients had at least one cardiovascular risk factor (smoking history, hypertension, diabetes, dyslipidemia, or obesity). However, recent studies establish that cardiotoxicity can also occur in this patient group. The time course of cardiotoxicity varies depending on patient age at the time of exposure and the class effect of chemotherapy drugs, where childhood cancer survivors experience exponentially increasing the risk for cardiovascular events ("late effect"); yet, the cardiovascular risk manifests earlier in older adults and is dependent on the number of conventional co-existing cardiac risk factors-hypertension in particular.

Cardiotoxicity is a dose-limiting and potentially lethal complication of anthracycline administration. Previous studies have failed to determine the definitive toxic doses or cardioprotective factors. Current dosing strategies may utilize the unnecessarily high anthracycline doses, such that survival benefits may not outweigh increased toxicity rates. The clinical significance of anthracycline cardiotoxicity is growing with increased cancer survivorship. Cardiotoxicity associated with anthracycline-based chemotherapies has limited its use in patients with pre-existing cardiomyopathy or heart failure.

This study aimed to evaluate the compatibility of the use of dexrazoxane with ASCO CPG recommendations as primary prophylaxis in the prevention of anthracycline-induced cardiotoxicity. It should be kept in mind that the retrospective design of the study is not suitable for determining whether dexrazoxane decreases the effectiveness of chemotherapy and its effectiveness as primary prophylaxis in the prevention of anthracycline-induced cardiotoxicity.

In recent years, anthracycline-induced cardiotoxicity has also been seen in patient populations at low risk of cardiac dysfunction. Therefore, larger randomized studies, including this patient population,

are warranted as they will help determine the treatment process in these patients.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

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