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Evaluation of Peripheral Blood Smear for Myelodysplasia in Breast Cancer Patients who Received Adjuvant Antracycline

Adjuvan Antrasiklin Rejimi Almış Remisyondaki Meme Kanserli Hastalarda Myelodisplazi Açısından Periferik Yayma Değerlendirmesi

Hasan Mutlu[1], Zeki Akca[2], Havva Uskudar Teke[3], Hediye Ugur[4]

[1]Department of Medical Oncology, Kayseri Education and Research Hospital, Kayseri, Turkey
[2]Department of Radiation Oncology, Mersin Govermant Hospital, Mersin, Turkey
[3]Department of Hematology, Kayseri Education and Research Hospital, Kayseri, Turkey
[4]Department of Internal Medicine, Kayseri Education and Research Hospital, Kayseri, Turkey

Abstract

Objective: Therapy-related myeloid neoplasms (t-MN) account for approximately 10% to 20% of all cases of AML (acute myeloid leukemia), MDS (myelodysplastic syndrome) and MDS/MPN (myelodysplastic syndrome/myeloproliferative neoplasms), MDS, and MDS/MPN. In our study, we evaluated peripheral blood smear samples and hemogram values in breast cancer patients who were receiving adjuvant anthracycline regimens and were in remission.

Materials and Methods: A total of 78 patients receiving anthracycline-based adjuvant chemotherapy treatment from Kayseri Research and Training Hospital and Mersin State Hospital were enrolled in the study. Their adjuvant treatments had been completed at least 18 months prior to the study.

Results: Two patients complained of anemia (2.2%) (Hb<11 mg/dl), leukopenia was observed in seven patients (7.7%) (leukocytes<4000/mm^3), and thrombocytopenia was observed in four patients (4.4%) (PLT<150.000/mm^3). In the blood smear samples, the following were observed: ovalomacrocytes (14%), macrocytes (37%), acanthocytes (1%), stomatocytes (12%), teardrops (12%), nucleated erythrocytes (1%), basophilic stippling (14%), and Howell-Jolly bodies (1%). Additionally, hypo-granulation (38%), Pelger-Huet abnormalities (26%), hypersegmentation (20%), immature granulocytes (8%), and blasts (6%) were observed. We also confirmed the presence of giant platelets (50%) and platelet hypogranulation (19%).

Conclusion: According to the peripheral blood smear assessments in our study, we suggest that breast cancer patients should be evaluated for MDS in the early stages, starting from month 18, even if the automated blood counts are normal.

Key Words: Anthracycline, Breast cancer, Chemotherapy side effect, Leukemia, Myelodysplasia

Özet

Amaç: Tedaviye bağlı myeloid neoplazmlar, tüm AML,MDS ve MDS/MPN vakalrının yaklaşık %10-20'sini oluşturmaktadır. Çalışmamızda adjuvant antrasiklinli kemoterapi rejimi almış remisyonda meme kanserli hastaların periferik yayma ve hemogram değerlerini araştırılmıştır.

Gereç ve Yöntem: Antrasiklin bazlı kemoterapi rejimi almış ve remisyonda olan toplam 78 hasta Kayseri Eğitim ve Araştırma Hastanesi ile Mersin Devlet Hastanesi'nden çalışmaya alınmıştır. Hastaların remisyonda olması ve tedaviyi en az 18 ay once tamamlamış olmasına dikkat edildi.

Bulgular: İki hastada anemi (%2.2) (Hb<11 mg/dl), 7 hastada lökopeni (%7.7) (Lökosit<4000/mm^3) ve 4 hastada trombositopeni (%4.4) (PLT<150.000/mm^3) saptandı. Ovalomakrositoz %14, makrositoz %37, akantositoz %1, stomatositoz %12, gözyaşı hücresi %12, çekirdekli eritrosit %1, bazofilik noktalanma %14 ve Howell-Jolly cisimciği %1 olarak tetkik edildi. %38 oranında hipogranülasyon, %26 Pelger-Huet anomalisi, %20 hipersegmentasyon, %8 immatür granülosit ve %6 blast vardı. Ayrıca %50 dev platelet ve %19 hipogranüle trombosit görüldü.

Sonuç: Çalışmamızın periferik yayma değerlendirme sonuçlarına gore meme kanserli hastaların myelodisplazik sendrom açısından, otomatik hemogram değerleri normal olsa da, erken dönemde, 18. aydan başlayarak rutin araştırılmasını önermekteyiz.

Anahtar Kelimeler: Antrasiklin, Meme kanseri, Kemoterapi yan etkisi, Lösemi, Myelodisplazi

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Correspondence to: Hasan Mutlu, Department of Medical Oncology, Kayseri Education and Research Hospital 38010, Kayseri, Turkey
Phone: +90 532 695 83 57 Fax: +90 352 320 73 13 e-mail: doktorhasanmutlu@gmail.com
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Introduction

Breast cancer is the most common tumor type in women [1]. The use of adjuvant chemotherapy to treat breast cancer has been extended over the past years from node-positive women to lower-risk patients [2, 3]. Anthracycline-containing chemotherapy has been shown to be more efficacious than alkylating-based chemotherapy and is currently the gold standard [4].

Leukemia and myelodysplasia (MDS) represent a small fraction of secondary cancers that are mainly associated with chemotherapy exposures. Therapy-related myeloid neoplasms (t-MN) account for approximately 10% to 20% of all cases of acute myeloid leukemia (AML), MDS, and MDS/MPN. Mitoxantrone, anthracyclines, epipodophyllotoxins, alkylating agents, antimetabolites, and spindle inhibitors are associated with AML/MDS [5-7].

Generally, topoisomerase-II inhibitors (e.g., mitoxantrone, anthracyclines, and epipodophyllotoxins) are significantly associated with an increased risk of AML/MDS. Several studies have suggested that anthracyclines and mitoxantrone increase the risk of AML and MDS in women who receive chemotherapy for breast cancer [8-12].

The latency period varies according to the chemotherapeutic agents administered. For example, after exposure to alkylating agents or radiation therapy, t-MN may occur in approximately five to seven years [13, 14]. After the use of topoisomerase II inhibitors, t-MN can develop after a shorter latency period of one to three years [15-17].

In our study, we evaluated peripheral blood smear samples and hemogram measurements in breast cancer patients who were receiving adjuvant anthracycline regimens and had been in remission for at least 18 months.

Materials and Methods

In our study, patients receiving anthracycline-based adjuvant chemotherapy treatment were evaluated. A total of 78 patients from Kayseri Research and Training Hospital and Mersin State Hospital were enrolled in the study. Their adjuvant treatments had been completed at least 18 months prior to the study. No patients had either chronic or infectious diseases. Patients with abnormal ferritin, vitamin B12 or folate levels were excluded from the study. The peripheral smear samples were evaluated by a hematologist. For statistical evaluations, SPSS 16.0 software was used.

Results

Patient characteristics are summarized in Table 1. All patients underwent 3, 4 or 6 courses of anthracycline-based adjuvant chemotherapy; 70% of the patients received epirubicin, and 30% were treated with adriamycin. Table 2 shows CBC parameters. The evaluations of peripheral blood smears are shown in Table 3.

Discussion

Recent MDS studies have generally enrolled patients with a median age of ≥65 years; there were more male patients than female patients [18, 19]. In MDS cases, subject to treatment, the median age of diagnosis was 61 [20]. The average age of the patients was 51 years old.

At the time of initial diagnosis, approximately 50% of MDS cases were asymptomatic [21, 22]. Some of the symptoms of MDS include anemia, neutropenia, thrombocytopenia, and bi-or pancytopenia. Anemia is observed in more than 80% of all MDS cases, leukopenia is established in 25-70% of all

Table 1. Patient characteristics

Parameter	n/Percentage	Mean	Median
Age	78 (100%)	52.7±9.6	51.0
Agent			
Anthracycline	23 (30%)	54.3±11.6	55.0
Epirubicin	55 (70%)	52.1±8.7	51.0
Number of cures			
3 or 4	31 (40%)	52.9±9.9	52.0
6	47 (60%)	52.6±9.5	51.0
Stage			
1	22 (28%)		
2	24 (30%)		
3	32 (41%)		
Receptor Status			
ER (+)	46 (63%)		
ER (-)	28 (36%)		
ER unknown	1 (2%)		
PR (+)	53 (68%)		
PR (-)	23 (30%)		
PR unknown	2 (2%)		
Cerb B2 (+)	25 (32%)		
Cerb B2 (-)	51 (66%)		
Cerb B2 unknown	2 (2%)		
Hormonal			
Tamoxifen	34 (44%)		
Aromatose inh.	27 (35%)		
No treatment	17 (21%)		

*Number of Cures; it means that number of regimen with antracycline that patients received. Abb: ER: Estrogen receptor, PR: Progesterone receptor

Table 2. CBC counts

Parameter (n=78)	Mean	Median	Minimum	Maximum
Hemoglobin	13	13	9	15
Leukocytes	6615	6259	3500	17500
Platelets	241000	242000	111000	435000
Neutrophils	58%	60%	37%	72%
Lymphocytes	30%	30%	17%	50%
Monocytes	7%	8%	1%	17%
Eosinophils	2%	1%	0%	19%
Basophils	0%	0%	0%	2%

Table 3. Results of peripheral blood smear assessments

Parameter (n=78)	Yes	No
Anemia	2 (2%)	76 (98%)
Leukopenia	7 (8%)	71 (92%)
Thrombocytopenia	4 (4%)	74 (96%)
Monocytosis	19 (24%)	59 (76%)
Red Blood Cells		
Ovalocytosis	11 (14%)	67 (86%)
Macrocytosis	29 (37%)	49 (63%)
Acanthocytosis	1 (1%)	77 (99%)
Stomatocytosis	9 (12%)	69 (88%)
Teardrops	10 (12%)	68 (88%)
Nucleated erythrocytes	1 (1%)	77 (99%)
Basophilic stippling	1 (1%)	77 (99%)
Howell-Jolly bodies	1 (1%)	77 (99%)
Granulocytic Series		
Pelger-Huet anomaly	0 (0%)	78 (100%)
Auer Rods	0 (0%)	78 (100%)
Hypogranulation	0 (0%)	78 (100%)
Nuclear Stick	0 (0%)	78 (100%)
Ringed-Shaped Nuclei	1 (1%)	77 (99%)
Hypersegmentation	23 (30%)	56 (70%)
Megakaryocytic Series		
Giant platelets	39 (50%)	39 (50%)
Hypogranular platelets	15 (19%)	63 (81%)

cases, and thrombocytopenia can be observed in 40-65% of all cases [21, 23, 24]. In our study, two patients complained of anemia (2.2%) (Hb<11 mg/dl), leukopenia was observed in seven patients (7.7%) (leukocytes<4000/mm^3), and thrombocytopenia was observed in four patients (4.4%) (PLT<150.000/mm^3). In our study, the number of patients with cytopenia was much lower than the number of patients diagnosed with MDS. However, because the patients in our study did not have co-morbidities, the percentage of cytopenia cases seemed to be important.

The most important signs of dyserythropoiesis, which were observed in the peripheral blood smears in the MDS cases, were the changes in the nuclei and the shapes of the erythrocytes. Among these symptoms in MDS patients, ovalomacrocytosis is one of the best described. During the evaluation process of our patients, it was established that there were ovalomacrocytes (14%), macrocytes (37%), acanthocytes (1%), stomatocytes (12%), teardrops (12%), nucleated erythrocytes (1%), basophilic stippling (14%) and Howell-Jolly bodies (1%) in the smears. The examination of MDS cases revealed 82% anisocytosis**,** 75% poikilocytosis, 57% teardrops, 17% nucleated erythrocytes, 38% basophilic stippling, and 8% Howell-Jolly bodies [25]. In one case report, the percentage of acanthocytes was approximately 5-10%. One patient participating in our study had acanthocytosis [26].

In myeloid series, the most important findings of myelodysplasia include hypo- and hypersegmentation, hypogranulation and the presence of blasts. Our study revealed 303 cases of hypersegmentation. In the aforementioned study, 38% hypogranulation, 26% Pelger-Huet abnormalities, 20% hypersegmentation, 8% immature granulocytes and 6% blasts were observed [25].

Giant platelets and platelet anisocytosis are the most important signs of dysthrombopoiesis that can be observed in the peripheral blood [23]. We observed the presence of giant platelets (50%) and platelet hypogranulation (19%). In another study, giant platelets and platelet anisocytosis were identified at frequencies of 46% and 26%, respectively [25].

The diagnosis of myelodysplasia must be made based on the evaluation of a peripheral smear. Granulocytic hypogranulation and hyposegmentation, hypochromia**,** polychromasia, nucleated and fragmented erythrocytes, macrocytosis, thrombocytic anisocytosis and giant platelets found in peripheral smears are important signs for establishing a diagnosis of myelodysplasia. However, an accurate diagnosis requires bone marrow aspiration and biopsy. Cytogenetic examination may help in making a diagnosis; however, normal results do not exclude the diagnosis. Chromosomal abnormalities are identified in 80% of t-MDS cases. In particular, in 70% of cases, 5q.7q and 20q deletions are observed. The chromosomal analysis will be required in this same group of patients.

Finally, according to the peripheral blood smear assessments of our study, we suggest that breast cancer patients should be evaluated for MDS in the early stages, starting from month 18, even if the automated blood counts are normal.

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