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Original scientific paper

Incidence of Febrile Neutropenia in Breast Cancer Patients Treated With Chemotheraphy Protocols From 01.01.2020 to 31.12.2021 in University Clinical Center of Republic of Srpska Banja Luka

Željka Cvijetić[1], Zdenka Gojković[2], Željko Jovičić[1], Sanja Kostur[1], Ilija Baroš[1], Slađana Šiljak[1]

[1]*Pan European-University Apeiron Banja Luka, Bosnia and Herzegovina, zeljkacvijetic@yahoo.com*

[2]*University Clinical Center of Republic of Srpska, Banja Luka*

ABSTRACT: Febrile neutropenia occurring during chemotherapy was reported to be a predictor of survival in breast cancer patients. We assessed the incidence of febrile neutropenia induced by chemotherapy. Data from a retrospective study on the application of chemotherapy protocols in breast cancer patients was reviewed. Analyzing the data, we can see that out of 81 patients who received chemotherapy, 43 were diagnosed with neutropenia and 4 or 9.3% of those patients were diagnosed with neutropenia again despite prophylaxis with Granulocyte-colony stimulating factor (G-CSF). In 4 or 9.3% of patients, further administration of that chemotherapy protocol had to be stopped due to severity of neutropenia and complications they caused. During the treatment, grade IV neutropenia was diagnosed in 27 or 63% of patients while grade I neutropenia was diagnosed in 2 or 4.65% of patients. Anemia associated with neutropenia was also diagnosed in 7 or 16.3% of patients while pancytopenia was diagnosed in 4 or 9.3% of patients, and thrombocytopenia associated with neutropenia was diagnosed in only one patient. The hazard ratio of febrile neutropenia presence compared to the absence of such toxicity was adjusted. The cox model was 0.75 (confidence interval 95% 0.54-0.95; P=0,0189) for grade I neutropenia, 0.63 (0.50-0.78; P<0,0001) for grade II neutropenia and 0.71 (0.51-0.98; P=0.3888) for grades III and IV neutropenia. These results suggest that the occurrence of neutropenia during chemotherapy is an independent predictor of increased survival in breast cancer patients, while the absence of such toxicity indicates that the drug doses are not sufficient. Monitoring of febrile neutropenia in patients treated with chemotherapy may contribute to improved drug efficacy and better survival rate.

Keywords: febrile neutropenia, breast cancer, chemotherapy protocols, side effects.

INTRODUCTION

The leading public health problem, in the world and in our country, are malignant diseases. They are in the second place after cardiovascular diseases, and they are responsible for the death of every fifth person in Republic of Srpska. Breast cancer is the most common malignant disease in women and the second most common cancer in the world. In Bosnia and Herzegovina the number of newly discovered cases is 1,152 per year and according to the data of Public Health Institute of the Republic of Srpska 450 to 480 women fall ill per year in Republic of Srpska. The incidence of growth is present from year to year.

It is considered that there are more than 2 million new cases of breast cancer in the world every year. Every 20 seconds, one woman in the world is diagnosed with breast cancer (Figure 2). In men, this type of cancer is quite rare (M:F-1:100).

The incidence of this cancer is different worldwide, it is rarely seen before the age of 30 then its incidence increases reaching its maximum around the age of 50. Recently, an increase in the number of patients in younger age groups has been noticed. Early diagnosis, genetic testings, innovative treatment methods, education of population on the importance of early detection, screening programs, recognition of risk factors (tobacco, obesity, physical inactivity, etc.) have caused the death rate to lag behind the increase in

the number of breast cancer patients. Thirty to fifty percent of deaths due to breast cancer can be prevented. Despite progress, breast cancer is still the most common cause of death in women aged 35 to 69.

The data for the period from 2005 to 2015 can be obtained from the Malignant Diseases Register of the Republic of Srpska on premature death for the age group 30-70 years old, classified by sex.

Prognosis of the disease for each patient is different and depends on a large number of factors. Members of the multidisciplinary team on the Consilium for malignant diseases use numerous pathological characteristics and biological behaviour of the tumor when making a decision on treatment, while also taking into account characteristics of the patients themselves and possible comorbidities. The most important prognostic factors are size of the tumor, status of the lymph nodes, pathohistological type of the tumor, HER2 status (which is also a predictor factor) and presence of metastasis.

After performing all diagnostic procedures and obtaining pathohistological confirmation of the disease, oncologist should determine the clinical TNM classification, based on which the stage of the disease is determined and the patient is sent to the multidisciplinary Consilium for malignant diseases.

Breast cancer chemotherapy can be neoadjuvant, adjuvant and systemic. Neoadjuvant chemotherapy is given in order to shrink the tumor mass and enable more effective surgical treatment. During implementation of neoadjuvant chemotherapy, it is necessary to monitor the clinical response to the therapy based on which the number of chemotherapy cycles is determined, for the maximum effect. Adjuvant chemotherapy is given to operated patients who have medium or high risk of disease recurrence. Application of this therapy reduces disease recurrence by up to 35%, and in elderly patients by up to 20%. Systemic therapy is used in the treatment of metastatic disease. The primary goal of this therapy is complete or partial remission of the disease. The secondary goal is to improve and maintain the quality of life and to prolong life, i.e. reduce the symptoms. It is applied as long as there is a response to the therapy.

Neutropenia in oncology patients is the most common and severe complication of chemotherapy and chemo/radiotherapy application, resulting from the myelosuppressive effect of cytostatics or radiation. It represents the biggest risk for the occurrence of infection which is associated with morbidity and mortality. Consequences of neutropenia are delay of chemotherapy and doses correction. It has been proven that reducing the dose by >25% leads to a smaller percentage of patients with complete regression and/or a shorter survival period. Neutropenia is an immune deficiency with a consequent high incidence of bacterial and fungal infections. There is a clear connection between the severity and duration of neutropenia and the frequency and type of infections. Neutropenia usually occurs during the first chemotherapy cycle and its intensity depends on the type of chemotherapy protocol, age, initial low number of neutrophils and absence of primary neutropenia prophylaxis. Cytostatics lead to the suppression of granulocytes, which in turn leads to significant damage of their DNA molecules. Neutropenia lasts between 7 to 14 days after chemotherapy administration, and the lowest values are expected after 10 days. As a result, patients need to have regular complete blood count and blood differential tests along with adequate monitoring between chemotherapy cycles. Oncology patients can be divided into 3 groups according to the risk of neutropenia occurrence: low, medium and high risk.

This division is based on the primary disease, current state (active disease or remission), neutropenia duration, chemotherapy exposure and immunosuppressive therapy intensity. According to the complication risk assessment related to infection, a decision on further therapy procedure is made. The Multinational Association of Supportive Care in Cancer (MASCC) has developed a recognition algorithm for patients in risk of developing infection related complications. Febrile neutropenia is a severe condition related to significant morbidity and mortality, and treatment costs. Even though the mortality has declined due to Granulocyte-colony stimulating factor, new generation antibiotics and antimycotics, its number is

still substantial. In patients with solid tumors the risk is 5% and in patients with comorbidities 24% to 84%. The American National Cancer Institute graded the toxicity criteria from 1 to 4.

In patients receiving Granulocyte-colony stimulating factor (G-CSF), reduced incidence, duration and severity of chemotherapy related neutropenia, incidence and mortality and reduced hospital stay due to febrile neutropenia have been demonstrated. Preventive G-CSF therapy enables full oncological therapy efficiency because there is no therapy prolongation and cytostatic dose reduction.

Granulocyte-colony stimulating factor (G-CSF) amplifies proliferation and differentiation of neutrophils, stimulates survival of mature neutrophils, increases phagocytic activity and cellular cytotoxicity. G-CSF in breast cancer therapy has improved disease free interval or disease-free survival. A meta-analysis of 17 randomized clinical trials showed that primary prophylaxis with G-CSF reduced the risk of febrile neutropenia and improved the dose intensity the patient received, along with a significant reduction in the risk of infection-related death. Another meta-analysis of 25 randomized clinical trials demonstrated improved survival in patients who received G-CSF primary prophylaxis. It is important to mention that the most common side effect of G-CSF is bone pain, which is easily absorbed. In order to introduce G-CSF to prophylactic purposes, the following should be considered: • type of chemotherapy • type of malignant disease • risk factors related to the patient • goal of therapy. According to the type of chemotherapy protocols and risk factors related to the patient, there is a classification of patients into: • high-risk (possibility of febrile neutropenia greater than 20%) • medium-risk (possibility of febrile neutropenia from 10 to 20%) • low-risk (possibility of febrile neutropenia less than 10%). After the first chemotherapy cycle, the patient is actively monitored and at each cycle a decision is made on the eventual inclusion of prophylaxis.

PURPOSE OF THE STUDY

To determine the total number of patients treated for breast cancer with diagnosed febrile neutropenia at the University Clinical Center Banja Luka, in the period from 01.01.2020 to 31.12.2021. To determine the most common degree of neutropenia and the most common form of treatment. To determine the most common chemotherapy protocol that caused neutropenia in patients, determine which preventive measures were taken in the further treatment and whether neutropenia was diagnosed again despite the taken measures.

MATHERIALS AND METHODS

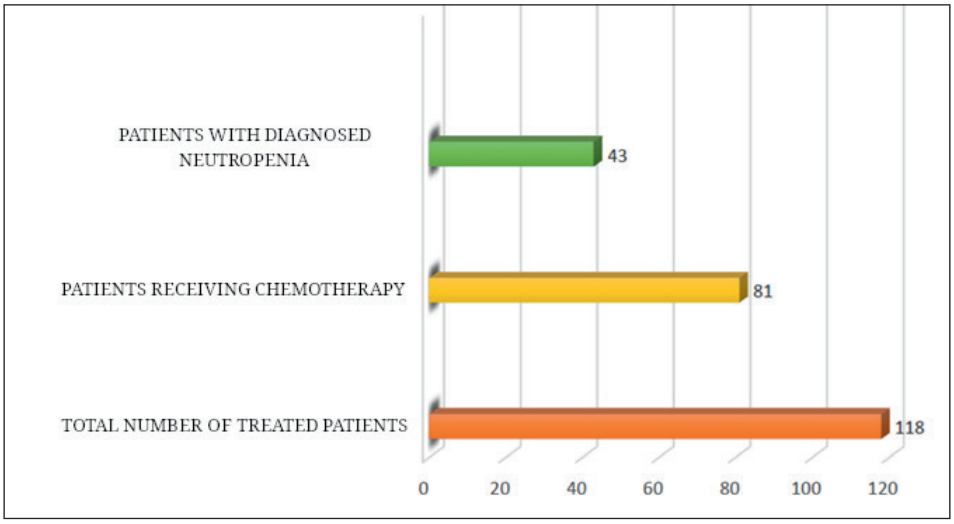
The examination of neutropenia incidence in patients with breast cancer is a retrospective study. The research was conducted in patients who suffered from breast cancer and received chemotherapy at the Oncology Clinic of the University Clinical Center of Republic of Srpska. The patients were observed in the period from 01.01.2020 to 31.12.2021. Data analysis identified patients diagnosed with neutropenia during chemotherapy. The study included 43 patients diagnosed with neutropenia during chemotherapy. The patients were stratified according to age, type of treatment, type of chemotherapy protocol, neutropenia degree, association of neutropenia with anemia and pancytopenia and taken preventive measures. The age of each patient was determined at the time of chemotherapy application. Type of therapy (neoadjuvant, adjuvant and systemic), chemotherapy protocols and preventive measures were determined based on patients` medical records and clinical information system. Neutropenia degree was determined based on the laboratory findings, so the patients were divided into four groups: grade I, grade II, grade III and grade IV. The association of neutropenia with anemia, thrombocytopenia and pancytopenia was also determined, and whether neutropenia was diagnosed again during further treatment. Preventive taken measures were determined from the patients` medical records and clinical information system.

RESULTS

Descriptive statistics

Frequency of neutropenia

In the observed period, 118 patients were treated for breast cancer, 81 received chemotherapy. Among these, 43 or 53.1% of patients were diagnosed with neutropenia at one point of treatment with cytostatic drugs.

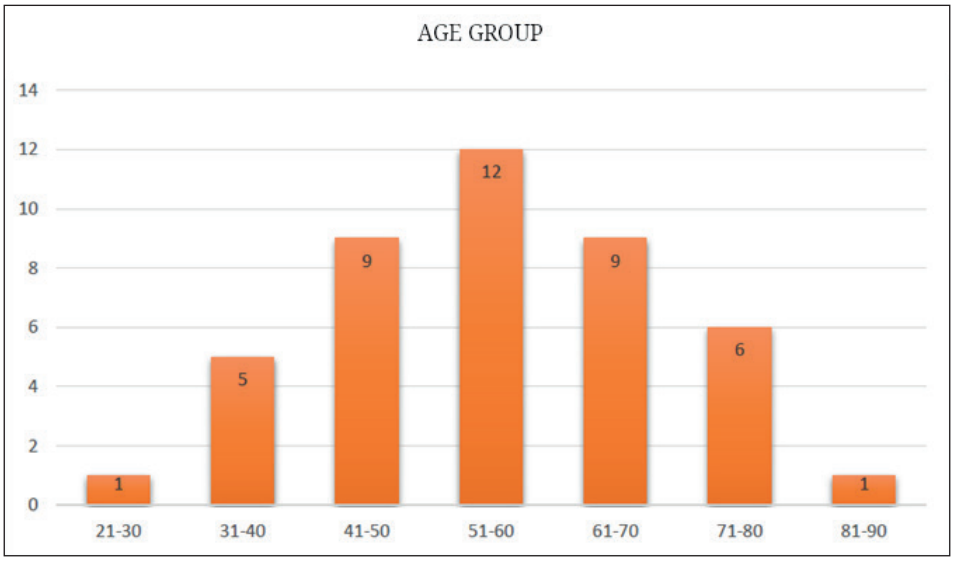


Graph 1. Display of patients treated at the Oncology Clinic of University Clinical Center of Republic of Srpska, 2020-2021

From Graph 1. we can see that about half of the patients were diagnosed with neutropenia. In addition, we will see which cytostatic drugs cause neutropenia the most.

Age group

The analysis included 43 patients diagnosed with neutropenia during chemotherapy. The youngest patient was 27 years old, while the oldest patient was 83 years old. The average age of patients was 54.

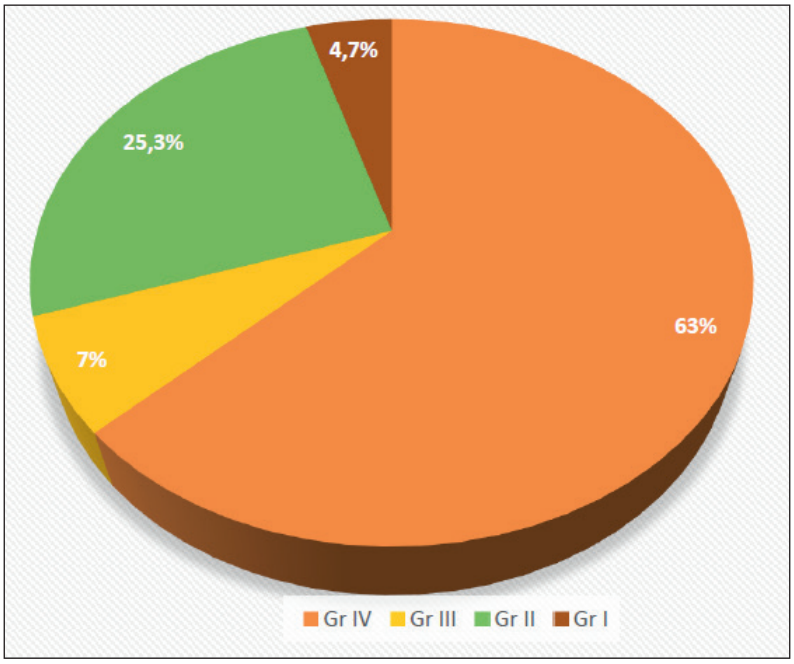


Graph 2. Display of female patients in relation to age

Graph 2. shows that the largest number of breast cancer patients with diagnosed neutropenia during chemotherapy was between 50 and 60 years old.

Grades of neutropenia

Grade IV neutropenia was diagnosed in 27 or 63% of patients, while grade I neutropenia was diagnosed in 2 or 4.65% of patients.

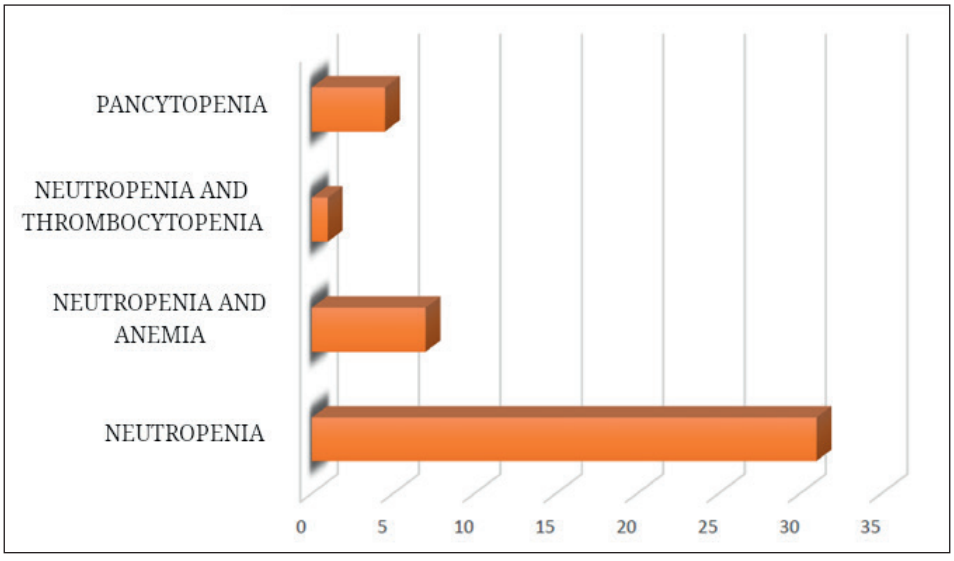


Graph 3. Display of patients in relation to grades of neutropenia

Graph 3. shows that the largest number of patients developed grade IV neutropenia during chemotherapy.

Association of neutropenia with anemia, thrombocytopenia and pancytopenia

Anemia associated with neutropenia was diagnosed in 7 or 16.3% of patients, pancytopenia was diagnosed in 4 or 9.3% of patients and thrombocytopenia associated with neutropenia in only one patient.

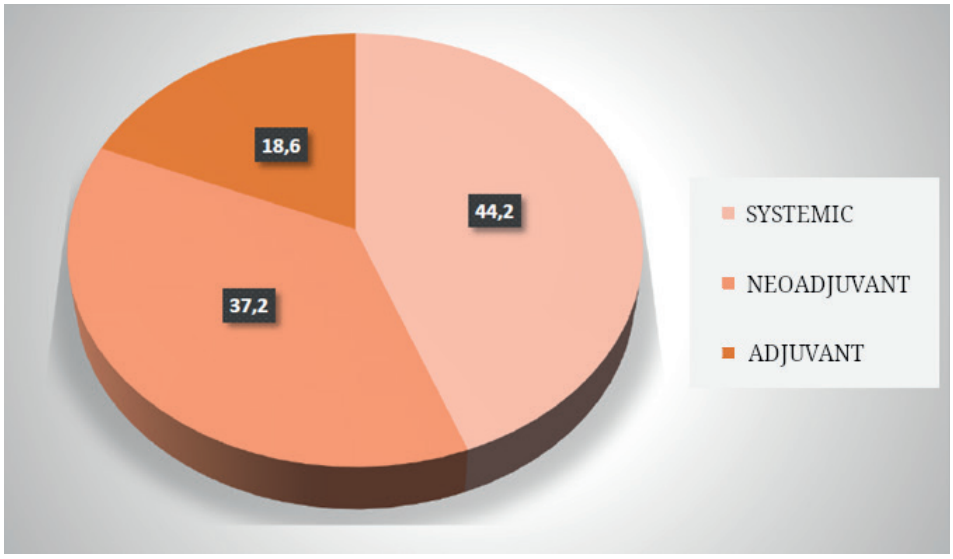


Graph 4. Display of female patients in relation to hematologic complications

Graph 4. shows that the largest number of patients had only neutropenia as a complication.

Types of treatment

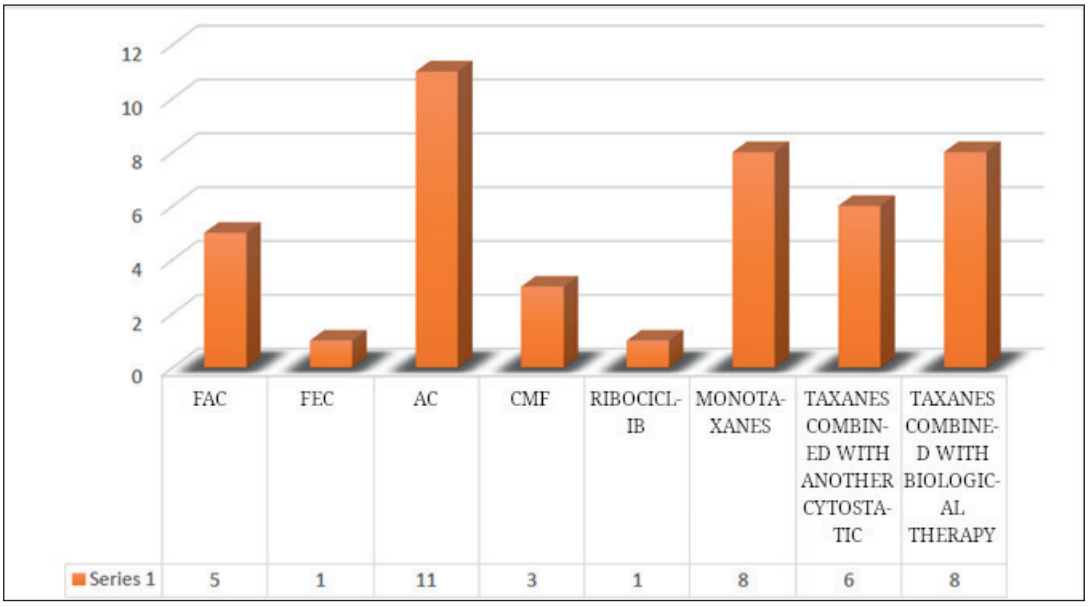
The largest number of patients, 19 or 44.2%, received systemic chemotherapy when diagnosed with neutropenia, 16 or 37.2 % of patients received neoadjuvant and only 8 or 18.6% adjuvant chemotherapy.



Graph 5. Types of treatment

Type of chemotherapy protocol

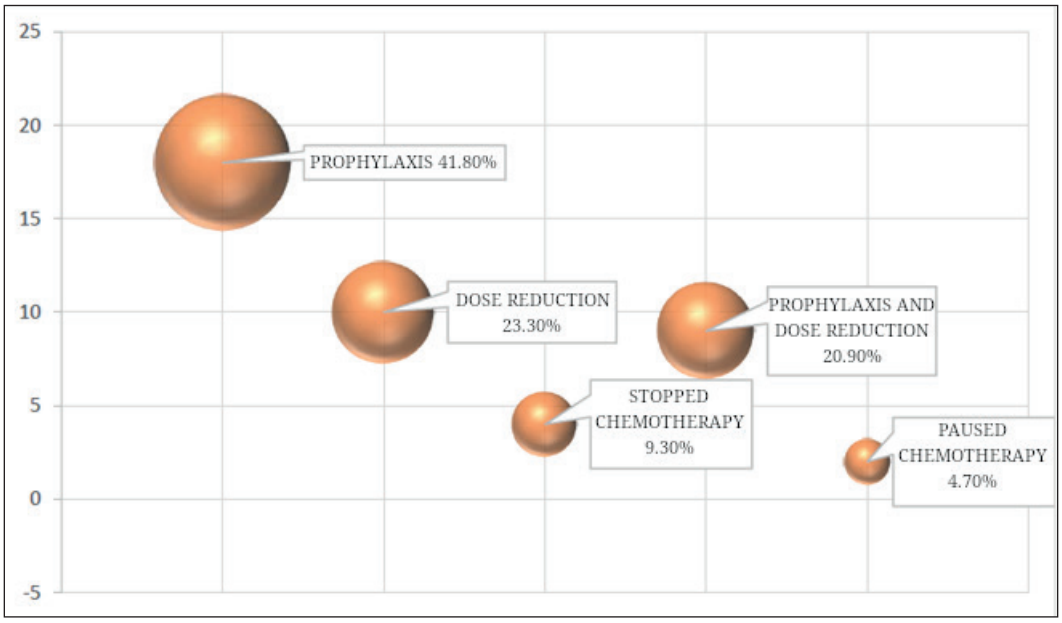
Analyzing chemotherapy protocols, we can see that the largest number of patients, 11 or 25.6%, received AC (adriamycin and cyclophosphamide) chemo protocol, and that two patients received FEC (flouracil, epirubicin and cyclophosphamide) and ribociclib, respectively.



Graph 6. shows that the largest number of patients received taxane-based chemotherapy, 22 or 51.2%.

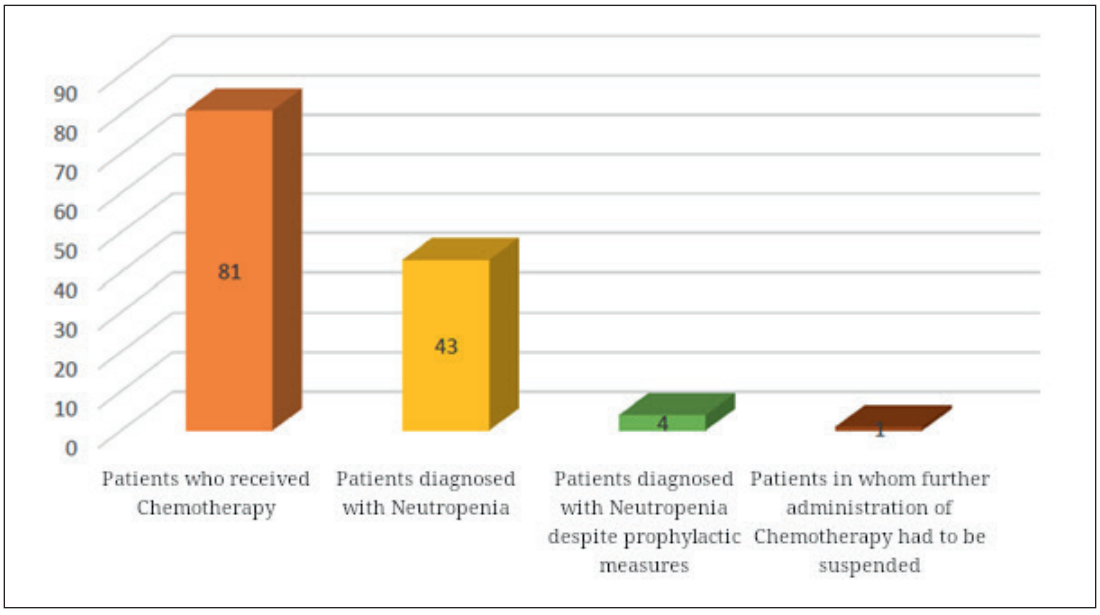
Preventive measures

In 18 or 41.8% of patients, preventive or prophylactic G-CSF was administered, dose reduction was performed in 10 or 23.3 % of patients while a combination of prophylaxis and dose reduction was introduced in 9 or 20.9% of patients.



Repeated neutropenia

Graph 8. shows that only four patients were diagnosed again with neutropenia and it is important to mention that only one patient had to stop further chemotherapy treatment due to a severe post-transfusion reaction.



Graph 8. Display of patients who were diagnosed again with neutropenia

The cox model was 0.75 (confidence interval 95% 0.54-0.95; P=0.0189) for grade I neutropenia, 0.63 (0.50-0.78 P<0.0001) for grade II neutropenia and 0.71 (0.51-0.98; P=0.3888) for grades III and IV neutropenia. These results suggest that the occurrence of neutropenia during chemotherapy is an independent predictor of increased survival in patients with breast cancer while the absence of such toxicity indicates that drug doses are not sufficient. Monitoring febrile neutropenia in patients receiving chemotherapy may contribute to improved drug efficacy and better overall survival.

DISCUSSION

Breast cancer is the most common malignant tumor and the most common cause of death from a malignant disease in female population. It is extremely rare in male population, only 1:100 cases compared to women. The incidence is different worldwide. Age is one of the main risk factors, with age the risk increases to reach its peak at the age of 50. Recently, an increase in the occurrence of this cancer in women under the age of 30 has been observed. It is not possible to influence the frequency of this cancer but it has been noted that the death rate has constantly been decreasing. Due to screening programs, innovative diagnostic procedures and new modalities of oncological treatment in developed countries, mortality has been reduced by 35%. Almost 50% of breast cancer is detected between 50 and 70 years old, while only 0.8% of breast cancer occurs in women under the age of 30, and about 6.5% in women between 30 and 40 years old. The youngest patient in our study was 27 at the time she received chemotherapy.

The average age of the patients was 54, which corresponds to the data from literature where it is stated that the risk of developing breast cancer increases with age and reaches its peak around the age of 50. Neutrophils represent the body`s main defense against infections. The severity of neutropenia is proportional to the risk of infection, so based on the number of neutrophils we distinguish between mild, moderate and severe. In patients receiving chemotherapy, the risk of neutropenia occurrence is between 7 and 14 days after chemotherapy administration. About 50% of patients who received chemotherapy at the Oncology Clinic of the University Clinical Center of the Republic of Srpska were at one point diagnosed with neutropenia. Based on this, we can conclude that our data match the literature.

From the observed sample, we can conclude that the largest number of neutropenia developed in patients during systemic therapy. We could not find any evidence in the literature that the type of therapy is a prognostic factor for neutropenia occurrence. Although we can find a justification in this data given that we know the systemic therapy is given in metastatic disease and that its aim is not to cure but to improve and prolong the quality of life. Bone marrow suppression is a common occurrence in the treatment of patients receiving taxane-based chemotherapy protocols. Neutropenia is a dose-dependent but also a dose-limiting toxicity. Like taxanes, adriamycin is a drug that has been shown to cause neutrophil depletion in 30% of patients between 7 and 14 days. In our sample, 22 or 51.2% of patients received taxane-based therapy and 16 or 32.1% received anthracycline (chemotherapy protocol with adriamycin), which is in accordance with the literature.

The multidisciplinary team at the Consilium for Malignant Diseases makes a decision on the further treatment based on the pathohistological findings of the primary tumor, available findings from diagnostic procedures, patient`s medical history and appearance. One of the decisions, after considering all mentioned above, is oncology treatment in the form of chemotherapy. Cytostatics are 29 drugs used in chemotherapy. Their role is to act on tumor cells and prevent them from dividing, growing and spreading further throughout the body. Unfortunately, as cytostatics act on tumor cells they also affect healthy cells in the body, so one of the complications of cytostatics is neutropenia. In our study, the largest number of patients, 27 or 62.9%, developed grade IV neutropenia, which is related to the fact that the largest number of patients received systemic therapy, and that 38 of the total number of patients received taxanes or anthracyclines which is consistent to the data from literature. Neutropenia prophylaxis using G-CSF has been beneficial in terms of reducing the frequency, duration and complications of neutropenia resulting from the chemo administration. The use of G-CSF enables regular application of therapy, without delaying chemo cycles. A large meta-analysis of 17 randomized clinical trials showed that primary prophylaxis with G-CSF reduced the risk of febrile neutropenia and showed a significant reduction in death rate. In the examined group of 43

patients, after diagnosed neutropenia, 18 or 41.8% continued to receive G-CSF for prophylactic purposes, 9 or 20.9 % continued to receive G-CSF and their cytostatic doses were reduced during the next chemotherapy cycle, while only four patients developed neutropenia again despite the prophylaxis and dose reduction.

CONCLUSION

At the Oncology Clinic of the University Clinical Center of the Republic of Srpska, 118 patients were treated during the observed period, of which 81 received chemotherapy and 43 were diagnosed with neutropenia. Breast cancer is most often detected in women aged 45 to 65. Half of the patients treated at the Oncology Clinic of the UKC RS were diagnosed with neutropenia during treatment. Grade IV neutropenia was diagnosed in the largest number of patients. The largest number of patients received systemic therapy. Chemotherapy based on taxanes and anthracyclines caused the highest number of diagnosed neutropenia. Prophylactic measures in most patients were prophylaxis with G-CSF and dose reductions. Only one patient had to stop further treatment administration of chemotherapy protocols due to repeated neutropenia and a severe form of post-transfusion reaction.

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