„CAROL DAVILA" UNIVERSITY OF MEDICINE AND PHARMACY
BUCHAREST
DOCTORAL SCHOOL
MEDICINE

MUSCULOSKELETAL MANIFESTATIONS OCCURING AFTER THE TREATMENTS OF ONCOLOGICAL CONDITIONS

THESIS SUMMARY

PhD Supervisor:
PROF. RUXANDRA IONESCU MD PhD

PhD Student:
GHINIA (Marr. CREŢU) IOANA

2023

Table of contents

Introduction **5**

GENERAL PART **6**

SPECIAL PART **6**

1. Study on musculoskeletal manifestations after targeted endocrine therapy of breast cancer with positive hormone receptors in postmenopausal patients **6**

1.1 Introduction 6

1.2 Materials and methods 7

1.3 Results 8

1.4 Discussions 24

1.5 Conclusions 25

2. Study on musculoskeletal adverse events in immunotherapy patients **26**

2.1 Introduction 26

2.2 Materials and methods 27

2.3 Results 28

2.4 Discussions 45

2.5 Conclusions 47

3. Conclusions and personal contributions **47**

References 52

Published papers 54

Introduction

The incidence of neoplasia continues to increase despite the efforts made for prevention, early detection and administration of treatment. Cancer treatment is a very complex process. In the past, treatment options were limited to chemotherapy, surgery and radiotherapy. However, in recent years, important progress has been made in terms of neoplastic therapy. New approaches include immune-mediated therapies and biological molecules. Hormone therapies are frequently used as they prevent tumor development by blocking hormone receptors.

Patient safety is an important element for the oncologist. The success of therapy lies in maintaining a balance between treatment, side effects and long-term survival. Monitoring patients and treating toxicities require the competence of oncologists and collaboration with specialist doctors from different fields. The evolution of treatments for neoplasms has led to innovations in supportive therapies [1].

Adverse events after oncological treatments are an important concern, both for the doctor and for the patient. Toxicities can lead to the disruption of the oncological treatment and can affect the quality of life of patients.

Through the development of new therapies, a new era in oncology has emerged. If until present, chemotherapy, surgery and radiotherapy aimed to destroy tumor cells, immunotherapy uses the immune system to fight cancer.

Immunotherapy represents an important discovery for the treatment of various solid tumors, increasing the life expectancy of patients with neoplasms. Currently, there are many types of immunotherapy, which can be administered to a large number of patients, but the survival rate in patients with advanced neoplasms is not greatly increased. This highlights the fact that the immune system is very complex, and research in this field continues. At present, new therapeutic targets and combined treatments are being explored [2].

The multidisciplinary approach of the patient with neoplasms is very important to counteract some unwanted effects of the therapies used. Both immunotherapy and hormone therapies can cause a series of musculoskeletal adverse events.

Musculoskeletal manifestations are varied: arthralgia, arthritis, polymyalgia rheumatica, rheumatoid arthritis, Sicca and Sjogren syndrome [3].

Considering that this is just the beginning of the use and development of cancer therapies, there will be many more studies in the future. These are necessary for the correct evaluation of musculoskeletal adverse events and for the correct estimation of the therapeutic benefits and toxicities.

I. GENERAL PART

This first part of the PhD thesis emphasizes cancer immunotherapy by reviewing its history, starting from the definition of cancer and ending with the explanation of the phenomenon of programmed cell death. The role of bacterial toxins, cytokines, monoclonal antibodies, immune checkpoint inhibitors, adoptive cell therapy, the regulation of cell-mediated immunity, the tumor microenvironment as a target for therapy in cancer immunotherapy are also analyzed.

With the understanding of negative regulatory pathways in cancer immunity, monoclonal antibodies and, in some cases, small molecules, have been developed for exploration in human clinical trials. Thus, the approved immune checkpoint inhibitor therapies were those with anti-CTLA-4 antibodies, such as Ipilimumab and Tremelimumab, but also anti PD-1/PD-L1 antibodies, such as Pembrolizumab, Nivolumab, Atezolizumab, Durvalumab, Avelumab and Pidilizumab.

Chapter 2 of the general part deals with the topic of endocrine therapy of breast cancer, justifying the important role of estrogen, tamoxifen, aromatase inhibitors (exemestane) and nonsteroidal aromatase inhibitors (Anastrozole and Letrozole). Also, in this chapter, the adverse events associated with hormone therapy are highlighted.

II. SPECIAL PART

1. Study on musculoskeletal manifestations after targeted endocrine therapy of breast cancer with positive hormone receptors in postmenopausal patients

1.1 Introduction

Treatments for neoplasms have evolved a lot in recent years and patient survival is much longer than in the past. Therapy for cancer patients includes chemotherapy, immunotherapy, hormone therapy, radiotherapy, and surgery. In this context, new challenges arise regarding the adverse events of oncological treatments. These manifestations occur quite frequently at the musculoskeletal level.

Breast cancer is the most common type of cancer diagnosed in women. There are no specific symptoms, the most common clinical sign being the presence of a painless lipoma that can form in the breast tissue. At diagnosis, the tumor is evaluated by molecular techniques to establish the presence of estrogen/progesterone receptors. Positive estrogen receptor (ER +) is found in most patients. The relationship between estrogen and breast cancer has been studied for a long time, and its carcinogenic effect consists in stimulating cell proliferation through ER [4].

Neoplasms that present endocrine receptors are sensitive to the presence of sex hormones, so they respond very well to reducing the production of sex hormones or blocking their effects at the receptor level [5]. Endocrine therapy with selective estrogen receptor modulators (SERMs) or aromatase inhibitors (AIs) is used in ER+ breast cancer. These two classes of drugs differ in their mechanism of action.

Tamoxifen is a selective estrogen receptor modulator, which will compete with estrogen to bind to the specific receptor [6].

In contrast, aromatase inhibitors will block the conversion of androgen to estrogen, thus reducing the serum concentration of estrogen [7]. AIs are divided into non-steroidal substances, such as anastrozole and letrozole, and steroidal ones, such as exemestane.

Musculoskeletal manifestations in women undergoing treatment with tamoxifen or IA usually include symmetric arthritis of the small joints of the hands, knees, hips, dorsolumbar spine, shoulders, which are accompanied by morning sickness. Other manifestations can be carpal tunnel syndrome, tenosynovitis, myalgia, decreased muscle strength.

The aim of this study was to emphasize the musculoskeletal manifestations that occurred after adjuvant endocrine therapy of breast cancer and to analyze the associated risk factors, diagnosis and treatment of rheumatological manifestations. Numerous risk factors that may worsen rheumatological manifestations were examined, namely body mass index (BMI), smoking, previous chemotherapy or radiation therapy, and stage of breast carcinoma.

1.2 Materials and methods

Women diagnosed with invasive ductal carcinoma or invasive lobular carcinoma with the presence of hormone receptors were included in the study. The 76 evaluated patients had stage 1, 2 and 3 invasive carcinomas. They received adjuvant treatment with letrozole 2.5 mg/day, anastrozole 1 mg/day, exemestane 25 mg/day or tamoxifen 20 mg/day. Among the 76 patients, 5 had a history of seropositive rheumatoid arthritis before the oncological diagnosis.

All 5 patients had background regimen for rheumatoid arthritis, being in remission.

The patients were initially evaluated by oncologists. The ones who had new joint or muscle pain after the administration of adjuvant endocrine therapy were referred to the rheumatologist for evaluation.

Laboratory analyzes were sampled to emphasize the inflammatory syndrome, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). All the patients were sampled for rheumatoid factor (RF) and uric acid.

Afterwards, the imaging examination was performed: ultrasound and Doppler ultrasound to emphasize synovitis, tenosynovitis, bursitis or enthesitis. Patients with joint pain had X-rays of the painful area.

The method was based on the graphical representation of quantitative and qualitative data.

1.3 Results

Age of patients

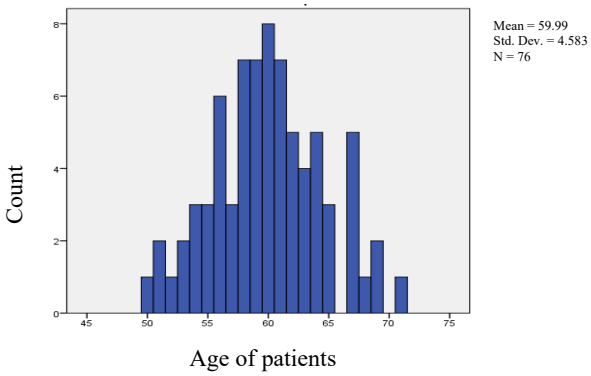

Fig. 1.1 Distribution of patients according to age

The mean age of the patients in this study was 59.9 years.

Smoking

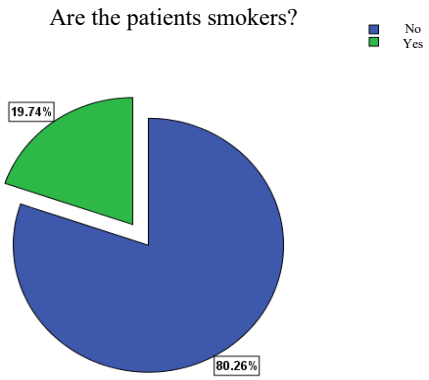

Fig. 1.2 Distribution of patients according to smoking

In this study, 19.74% of the patients were smokers. The patients who did not smoke at the time of the evaluation, but who were smokers in the past, were also mentioned as smokers.

Body mass index (BMI)

50% of the patients had a BMI between 8.5 kg/m2 and 24.9 kg/m2, being of normal weight, and 50% of the patients had a BMI between 25 kg/m2 and 29.9 kg/m2, being overweight.

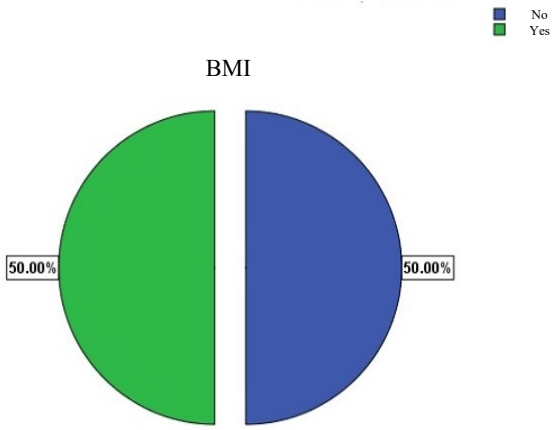

Fig. 1.3 Distribution of patients according to BMI

Fig. 1.4 shows that 16 of the overweight patients had stage 1 breast cancer, 14 patients had stage 2 breast cancer and 8 overweight patients had stage 3 breast cancer.

There was a statistically significant correlation between overweight patients and cancer (Chi-square =13.03, p=0.001).

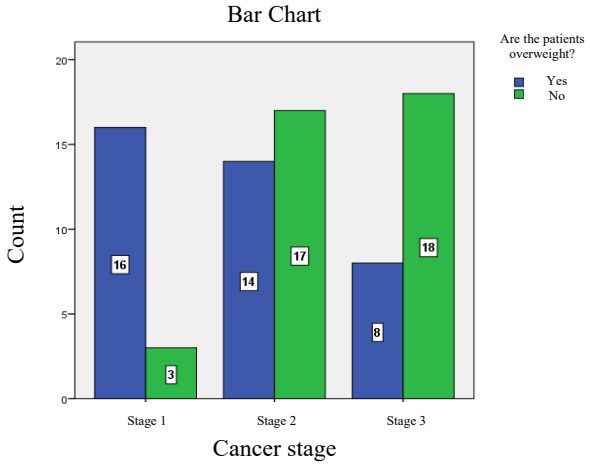

Fig. 1.4 Distribution of patients according to the stage of breast and BMI

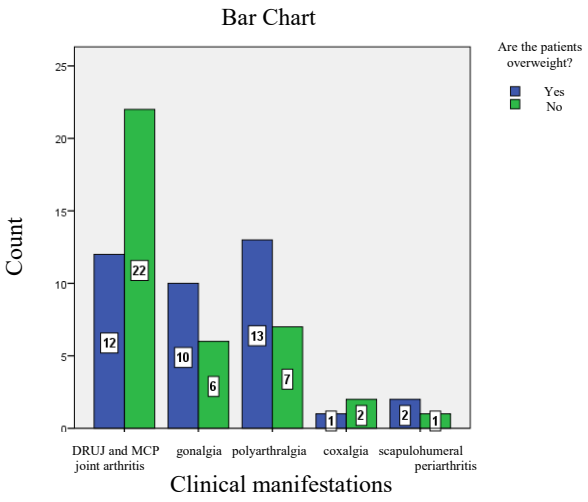

Fig. 1.5 Distribution of patients according to the type of clinical manifestations and BMI

The distribution of patients according to BMI and clinical manifestations can be observed in fig. 1.5. Thus, 12 overweight and 22 normal weight patients had DRUJ and MCF joint arthritis. 10 overweight patients and 6 patients with normal BMI had gonalgia. 13 overweight and 7 normal weight patients had polyarthralgia. Coxalgia occurred in one overweight patient and 2 patients with normal BMI. Scapulohumeral periarthritis occurred in 2 overweight patients and one normal weight patient.

Bone densitometry (DXA score)

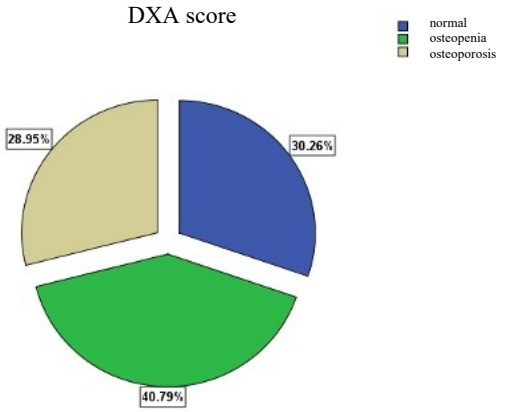

Fig. 1.6 Distribution of patients according to DXA score

Fig. 1.6 shows that 28.95% of the patients had osteoporosis, 40.79% had osteopenia and 30.26% had normal DXA values.

Among the 22 patients with osteoporosis, 4 patients were receiving bisphosphonate treatment before the diagnosis of breast cancer.

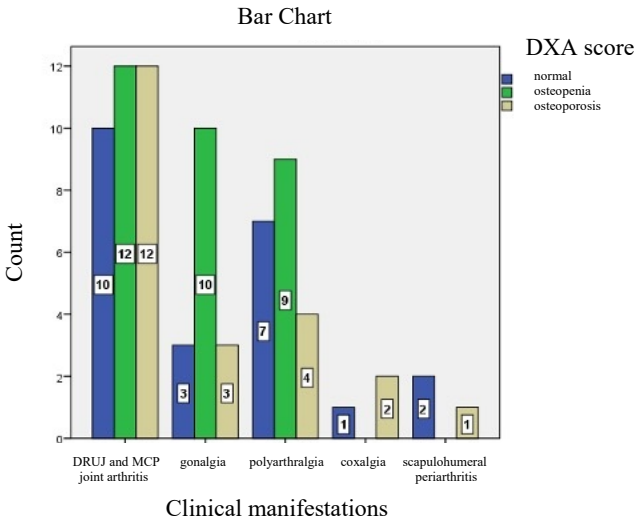

Fig. 1.7 Distribution of patients according to the stage of breast cancer

According to fig. 1.7, most of the patients diagnosed with stage 1 breast carcinoma had normal values of bone densitometry (14 patients). 18 patients with osteopenia had stage 2 breast cancer, and 15 patients with osteoporosis had stage 3 breast cancer.

There was a statistically significant correlation between the different cancer types and DXA scores (Chi-square = 33.23, p=0.001). Thus, there was an association between the presence of osteopenia and stage 2 cancer and osteoporosis and stage 3 cancer.

Hormone therapy

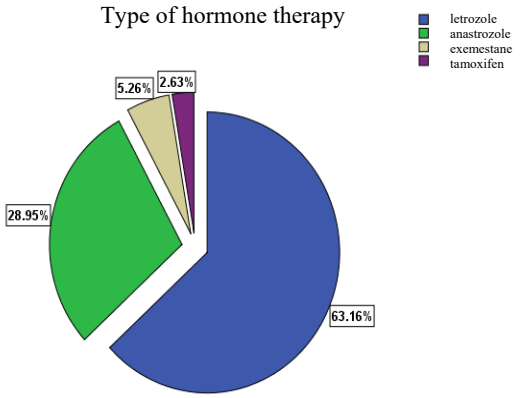

Fig. 1.8 Distribution of patients according to adjuvant endocrine therapy

Fig. 1.8 shows that 63.16% of the patients were treated with letrozole, 28.95% with anastrozole, 5.26% with exemestane, and 2.63% with tamoxifen.

Clinical manifestations

According to fig. 1.9, the most frequent clinical joint manifestations after endocrine adjuvant therapy of breast cancer were DRUJ and MCP joint arthritis (44.74%). 26.32% of the

patients had polyarthralgia, 21.05% had gonalgia, 3.95% had coxalgia and 3.95% had scapulohumeral periarthritis.

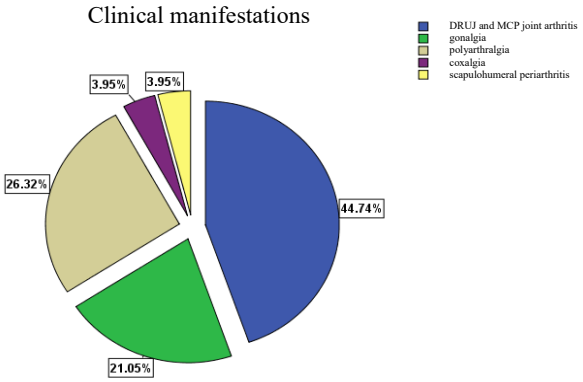

Fig. 1.9 Distribution of patients according to musculoskeletal manifestations

Fig. 1.10 shows the distribution of clinical manifestations according to the adjuvant hormone therapy. Among the patients with DRUJ and MCP joint arthritis, 24 were treated with letrozole, 9 with anastrozole and one patient with tamoxifen. Gonalgia occurred in 10 patients treated with letrozole, 5 treated with anastrozole and one treated with exemestane. Polyarthralgia occurred in 10 patients treated with letrozole, 7 with anastrozole, 2 with exemestane and one with tamoxifen. Coxalgia occurred in 2 patients treated with letrozole and one patient treated with anastrozole. Scapulohumeral periarthritis occurred in 2 patients treated with letrozole and one patient treated with exemestane.

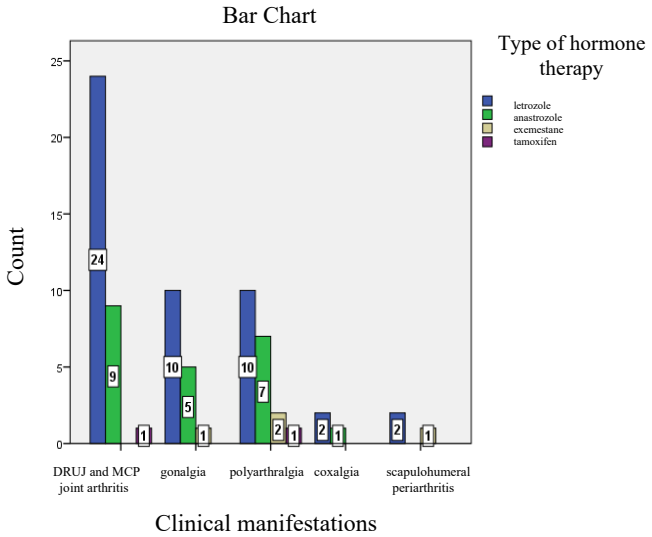

Fig. 1.10 Distribution of clinical manifestations according to the type of hormone therapy

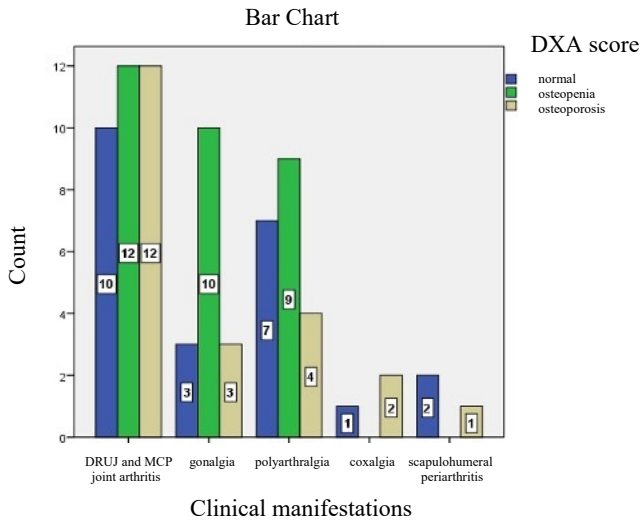

Fig. 1.11 Distribution of clinical manifestations according to the DXA score

Fig. 1.11 shows the distribution of clinical manifestations according to bone densitometry. Among the patients who had osteoporosis, 12 had hand arthritis, 3 had gonalgia, 4 polyarthralgia, 2 coxalgia and one patient with osteoporosis had scapulohumeral periarthritis.

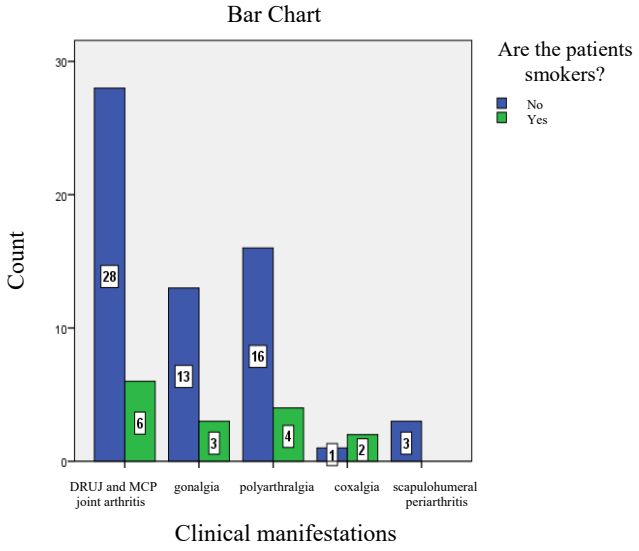

Fig. 1.12 Distribution of clinical manifestations according to smoking

Fig. 1.12 shows the distribution of clinical manifestations according to the smoking status. Among the patients who had DRUJ and MCP joint arthritis, 28 were smokers and 6 were non-smokers. Gonalgia occurred in 13 smoking patients and 3 non-smoking patients. 16 smoking patients had polyarthralgia and only 4 non-smoking patients had polyarticular pain. In the case of coxalgia patients, 2 were non-smokers and one was a smoker. Scapulohumeral periarthritis occurred in 3 smoking patients.

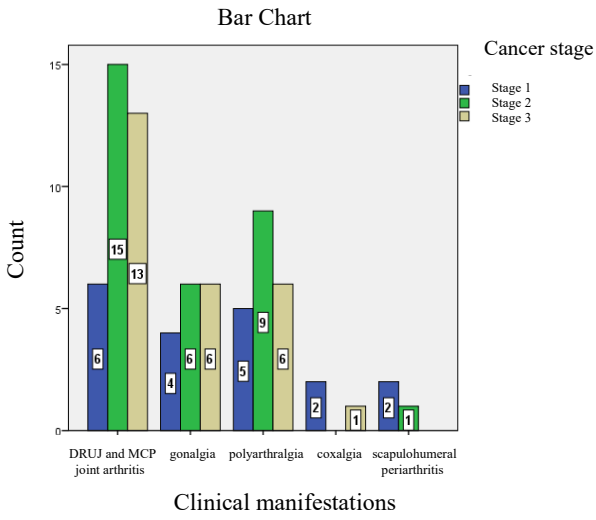

Fig. 1.13 Distribution of clinical manifestations according to the breast cancer stage

Fig. 1.13 shows the distribution of clinical manifestations according to the breast cancer stage. The patients who had stage 3 breast cancer most frequently had DRUJ and MCP joint arthritis (13 patients), 6 patients had gonalgia, 6 patients had polyarthralgia and one patient had coxalgia. Most patients with stage 2 breast cancer [8] had DRUJ and MCP joint arthritis, 9 had polyarthralgia, 6 gonalgia and one scapulohumeral periarthritis. Patients with stage 1 breast cancer most frequently had DRUJ and MCP joint arthritis [9], 5 had polyarthralgia, 4 gonalgia, 2 coxalgia and 2 scapulohumeral periarthritis.

Onset of clinical manifestations

According to fig. 1.14, the onset of clinical manifestations was on average 3 months after the initiation of endocrine adjuvant treatment. Most patients had joint pain 2 months after starting the treatment. The earliest arthralgia occurred after 1 month of adjuvant therapy and the latest after 1 year of therapy.

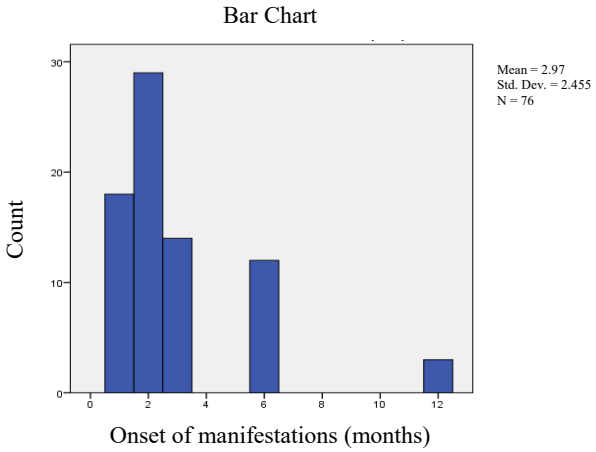

Fig. 1.14 Distribution of patients according to the onset of manifestations

Breast cancer stage

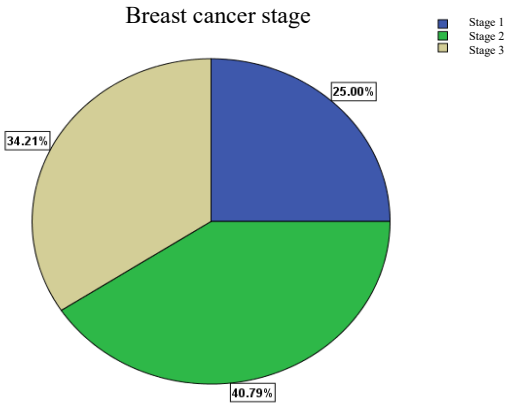

Fig. 1.15 Distribution of patients according to the breast cancer stage

Fig. 1.15 shows that 25% of the patients had stage 1 breast cancer, 40.79% had stage 2 breast cancer, and 34.21% had stage 3 breast cancer.

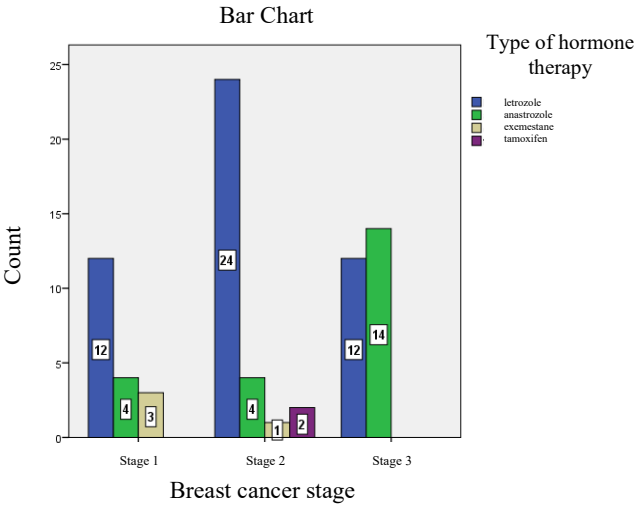

Fig. 1.16 Distribution of patients according to the of breast cancer stage and hormone therapy

Chemotherapy

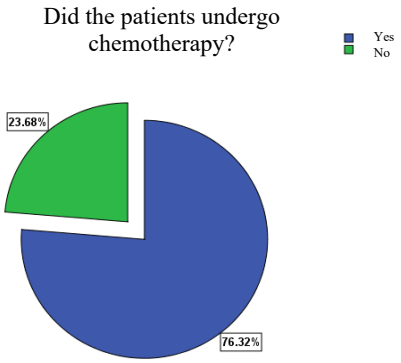

Fig. 1.17 Distribution of patients according to chemotherapy

Fig. 1.17 shows that 76.32% of the patients with breast cancer underwent chemotherapy.

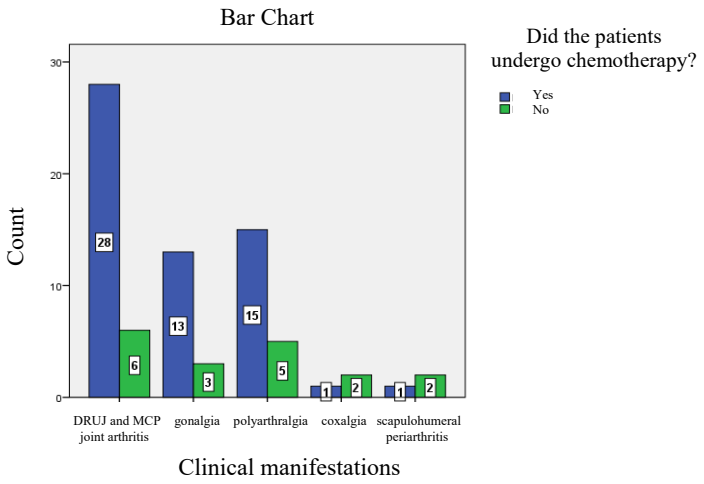

Fig. 1.18 Distribution of patients according to clinical manifestations and chemotherapy

Fig. 1.18 shows the distribution of clinical manifestations according to the chemotherapy regimen. Most of the patients who underwent chemotherapy [10] had DRUJ and MCP joint arthritis, 15 patients had polyarthralgia, 13 gonalgia, one patient had coxalgia and one patient had scapulohumeral periarthritis.

There was a statistically significant correlation between cancer stages and the application of chemotherapy-based regimen (Chi-square = 70.75, p=0.001). Thus, patients with stages 2 and 3 cancer followed a chemotherapy-based regimen.

Radiotherapy

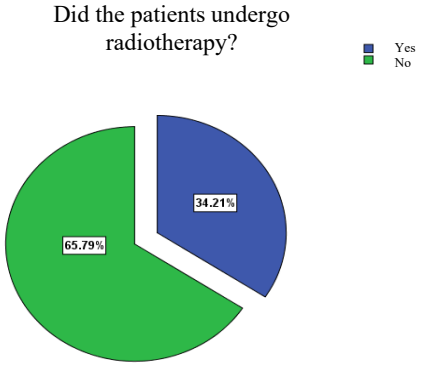

Fig. 1.19 Distribution of patients according to radiotherapy

Fig. 1.19 shows that 34.21% of the patients with breast cancer underwent radiotherapy.

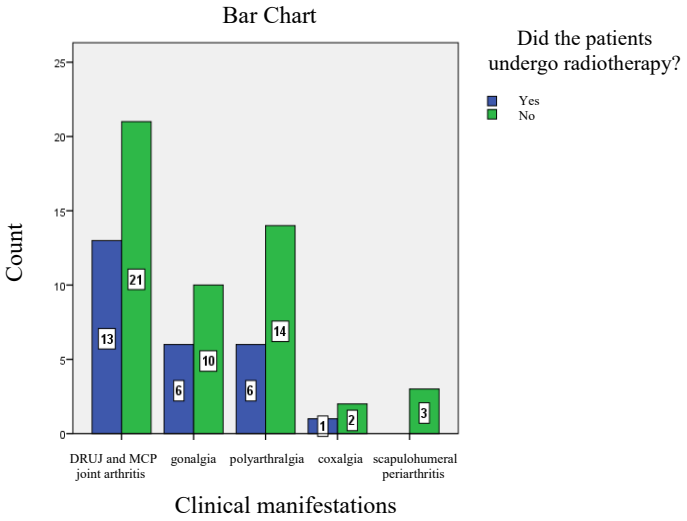

Fig. 1.20 Distribution of patients according to clinical manifestations and radiotherapy

Fig. 1.20 shows that 13 of the patients who underwent radiotherapy had DRUJ and MCP joint arthritis, 6 had gonalgia, 6 had polyarthralgia and one patient had coxalgia.

There was a statistically significant correlation between cancer stages and the application of a treatment based on radiotherapy (Chi-square = 76.00, p=0.001). Thus, patients with stage 3 cancer followed a treatment based on radiotherapy.

Rheumatology diagnosis

36 patients were diagnosed with hand arthritis. They did not have the diagnosis before the initiation of adjuvant treatment for breast cancer. Bilateral hand X-rays were performed in antero-posterior incidence to all the patients who had arthritis of the hands. Arthritic changes were identified, especially the narrowing of the distal interphalangeal (DIP), proximal inter-phalangeal (PIP), carpometacarpal I (CMC I) joint spaces, osteophytes and subchondral sclerosis joints.

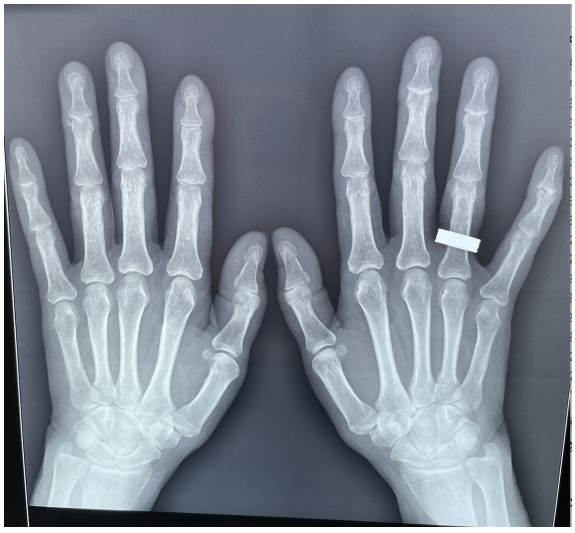

Fig. 1.21 X-ray of a patient with arthritis of the hands

Fig. 1.21 shows an antero-posterior X-ray of a patient diagnosed with arthritis of the hands. Narrowing of the PIP joint spaces, bilateral DIP, the presence of osteophytes and osteosclerosis can be observed.

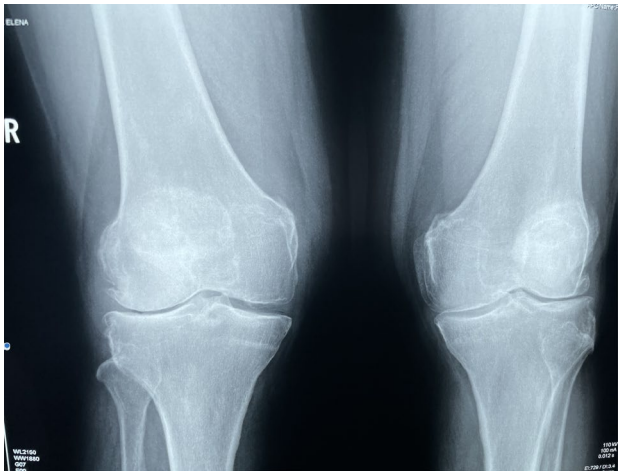

Fig. 1.22 X-ray of a patient with bilateral gonarthrosis

Fig. 1.22 shows a knee X-ray in antero-posterior incidence of a patient with stage 3 gonarthrosis. Narrowing of the joint space in the bilateral medial and lateral compartment, osteosclerosis of the tibial spine and the presence of osteophytes can be observed.

Among the 76 patients, 4 predominantly had nocturnal paresthesias in the hands. Phalen test was performed and it was positive in all patients.

3 patients were diagnosed with bilateral subscapularis calcific tendonitis. These patients had scapulohumeral periarthritis.

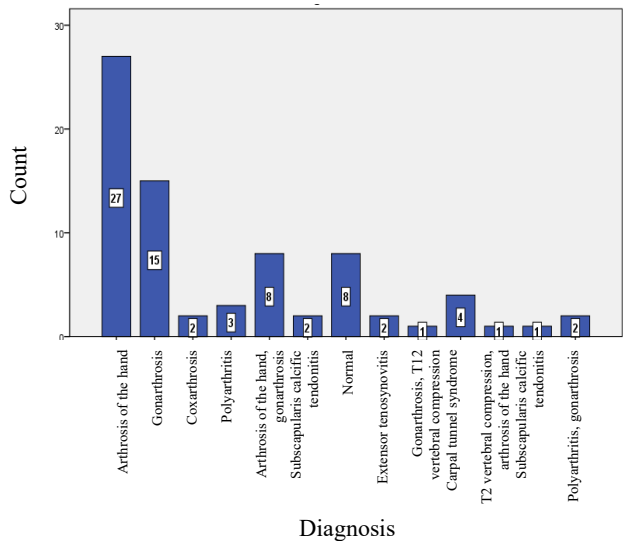

Fig. 1.23 Distribution of patients according to diagnosis

5 patients had a rheumatological history of seropositive rheumatoid arthritis. These patients did not present any symptoms of the disease in the year preceding the evaluation. They had new polyarticular joint pain after the initiation of the aromatase inhibitor treatment, especially mixed type gonalgia and morning stiffness, approx. 15 minutes. The symptoms occurred between 1 month and 3 months after starting the treatment. All patients underwent chemotherapy. Two patients out of the 5 were diagnosed with gonarthrosis.

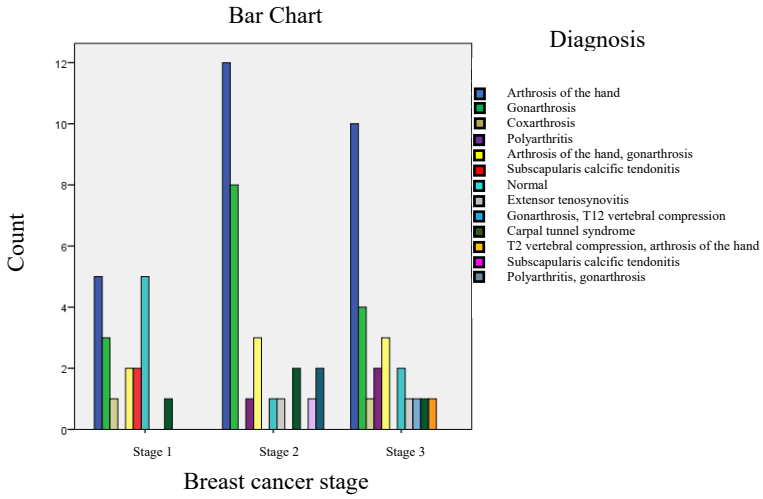

Fig. 1.24 Distribution of patients according to diagnosis and breast cancer stage

The quality of life assessment questionnaire (QOLQ)

For the assessment of functional capacity and pain, it was decided that the QOLQ questionnaire with 8 questions regarding the patients' daily activities should be applied.

The QOLQ score was applied at the first assessment. 48 patients had mild-moderate impairment, 24 patients had moderate-severe impairment and 4 patients had severe impairment. After treatment, the QOLQ score was applied again (on average 1 month after the first patient assessment), 67 patients having mild-moderate impairment, and 9 patients having moderate-severe impairment.

Fig. 1.25 shows the distribution of patients according to age and QOLQ score value at first presentation.

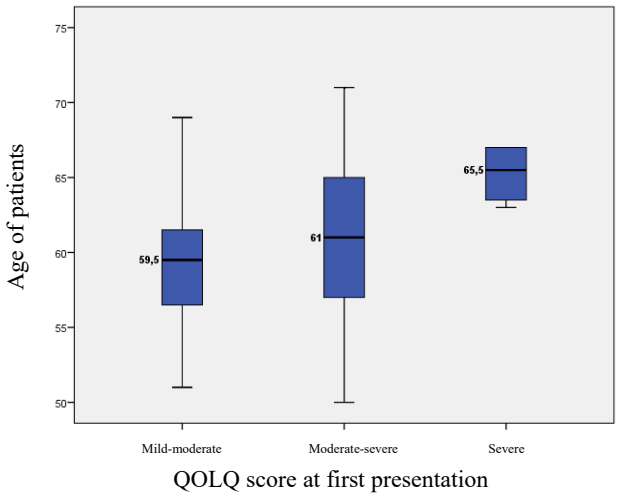

Fig. 1.25 Distribution of patients according to QOLQ score at first presentation and age

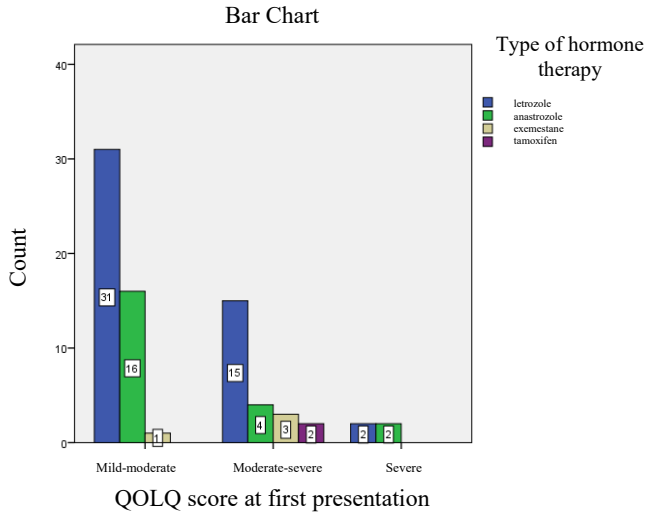

Fig. 1.26 Distribution of the QOLQ score at first presentation according to the hormone therapy

Fig. 1.26 shows the distribution of the QOLQ score according to the type of hormone therapy, thus 31 patients treated with letrozole, 16 patients treated with anastrozole and one patient treated with exemestane had a mild-moderate score. 15 patients treated with letrozole, 4 with anastrozole, 3 with exemestane and 2 with tamoxifen had a moderate-severe score. 2 patients following treatment with letrozole and 2 with anastrozole had a severe score.

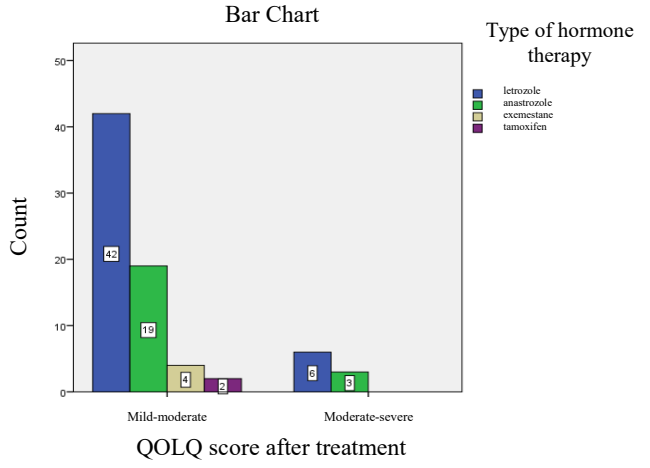

Fig. 1.27 Distribution of the QOLQ score after treatment according to the type of hormone therapy

Fig. 1.27 shows the distribution of the QOLQ score after treatment according to the type of hormone therapy. It could be observed that there were no patients with severe impairment. Among those with mild-moderate impairment, 42 patients were treated with letrozole, 19 with anastrozole, 4 with exemestane and 2 with tamoxifen. Among the patients with moderate-severe impairment, it was observed that 6 were treated with letrozole and 3 with anastrozole.

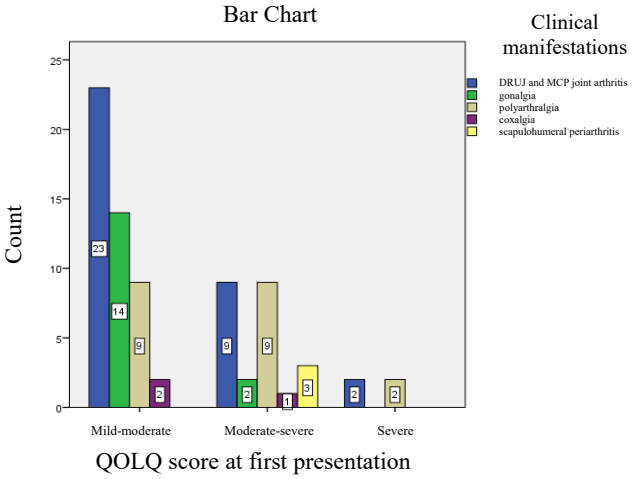

Fig. 1.28 Distribution of QOLQ score at first presentation according to clinical manifestations

Fig. 1.28 shows the QOLQ score at first presentation according to clinical manifestations. 23 patients with DRUJ and MCP joint arthritis, 14 patients with gonalgia, 9 with polyarthralgia and 2 with coxalgia had mild-moderate impairment. 8 patients with DRUJ and MCP joint arthritis, 2 patients with gonalgia, 9 with polyarthralgia, one with coxalgia and 3 patients with scapulohumeral periarthritis had moderately severe impairment. 2 patients with DRUJ and MCP joint arthritis and 2 patients with polyarthralgia had severe impairment of the quality of life.

Among the patients with rheumatoid arthritis, 4 had moderate-severe impairment and one patient had mild-moderate impairment.

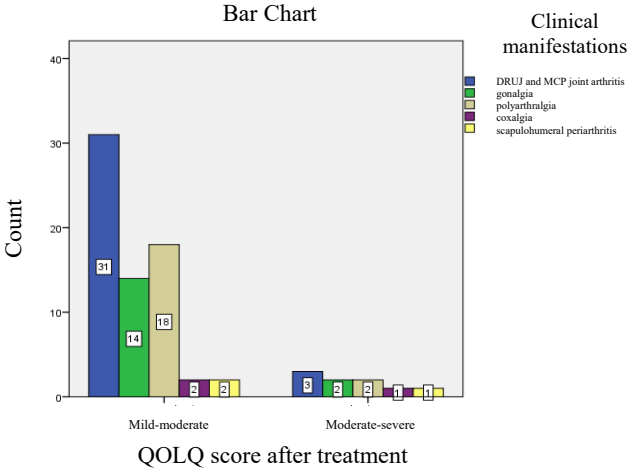

Fig. 1.29 Distribution of the QOLQ score after treatment according to clinical manifestations

Fig. 1.29 shows the QLOQ score applied after the treatment. 31 patients with DRUJ and MCP joint arthritis, 14 patients with gonalgia, 18 patients with polyarthralgia, 2 patients with coxalgia and 2 patients with scapulohumeral periarthritis had mild-moderate impairment. 3 patients with DRUJ and MCP joint arthritis, 2 patients with gonalgia, 2 patients with polyarthralgia, 1 patient with coxalgia and 1 patient with scapulohumeral periarthritis had moderate-severe impairment. After the treatment, there were no patients with severe impairment of the quality of life.

Treatment

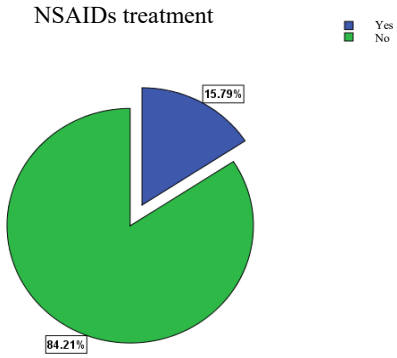

Fig. 1.30 Distribution of patients according to NSAIDs treatment

Fig. 1.30 shows the distribution of patients according to the administration of NSAIDs treatment. 84.21% of the patients underwent NSAIDs treatment. The treatment was administered for short periods in the lowest dose. There were patients who could not be administered NSAIDs due to associated digestive or cardiovascular pathology.

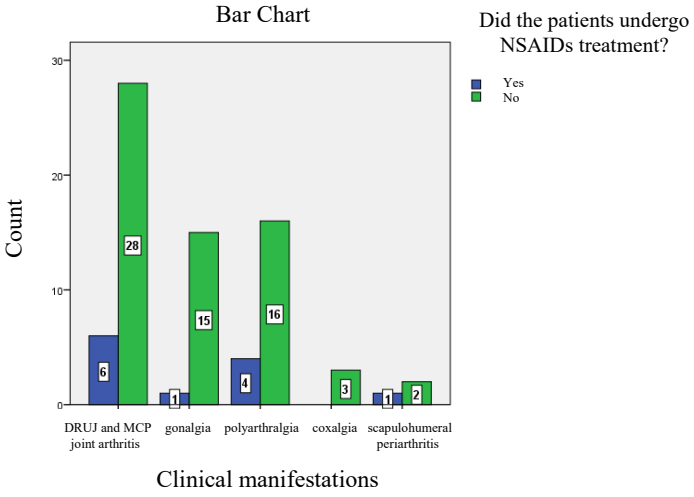

Fig. 1.31 Distribution of clinical manifestations according to NSAIDs treatment

Fig. 1.31 shows the distribution of clinical manifestations and NSAIDs treatment. Among the patients with DRUJ and MCP joint arthritis, 6 were treated with NSAIDs, as well as one patient with gonalgia, 6 of the patients with polyarthralgia and one patient with scapulohumeral periarthritis.

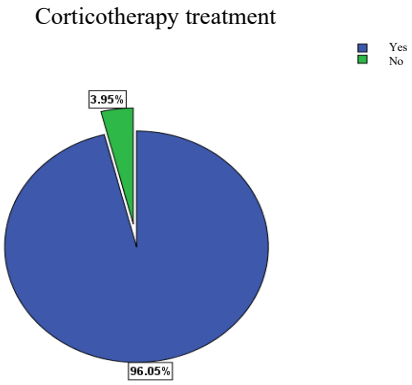

Fig. 1.32 Distribution of patients according to corticotherapy treatment

Fig. 1.32 shows that 3.95% of the patients were treated with corticotherapy.

Fig. 1.33 shows the distribution of patients according to cortisone treatment and clinical manifestations.

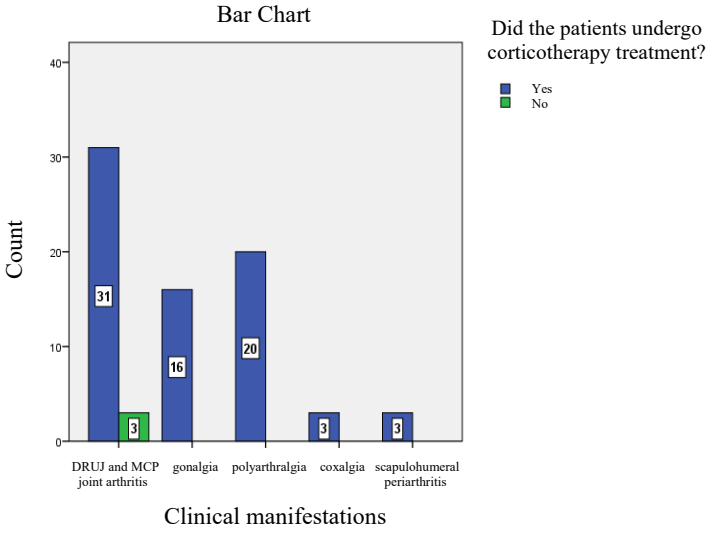

Fig. 1.33 Distribution of patients according to corticotherapy and clinical manifestations

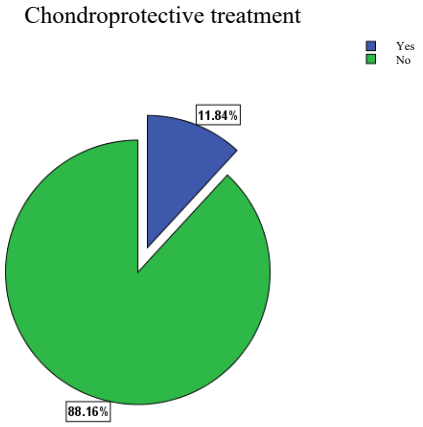

Fig. 1.34 Distribution of patients according to chondroprotective treatment

Fig. 1.34 shows that 88.16% of the patients underwent treatment with chondroprotective drugs.

Patients with a history of rheumatoid arthritis maintained the background regimen throughout the period of the oncological treatments. The patients were treated with methotrexate between 10 mg and 20 mg per week and another patient was treated with leflunomide 20 mg/week.

In addition to the treatment with NSAIDs, vitamin D3, bisphosphonate, chondroprotective drugs, treatment with omega 3 fatty acids was recommended for all patients.

1.4 Discussions

Aromatase inhibitors have been used more and more frequently in recent years as adjuvant treatment in breast cancer in women. In addition to the patients who were treated with letrozole, anastrozole and exemestane, 2 patients who were treated with tamoxifen were evaluated in this study. 76 patients with breast cancer with estrogen receptors were treated with adjuvant hormone therapy. Among the 76 patients, there were 5 who had a history of seropositive rheumatoid arthritis, under a background regimen.

It is difficult to compare arthralgia induced by treatment with tamoxifen or aromatase inhibitors with other causes of joint pain. The most commonly affected are DRUJ and MCP joint arthritis, knees and shoulders. Carpal tunnel syndrome or tenosynovitis may occur.

36 patients were diagnosed with arthritis of the hand, 25 patients with gonarthrosis, 4 patients with bilateral carpal tunnel syndrome, 3 patients with bilateral subscapularis calcific tendonitis, 2 patients with T12 vertebral compression, 2 patients with bilateral hand extensor tenosynovitis and 2 patients with bilateral coxarthrosis. The patients who had a history of rheumatoid arthritis had mixed type polyarthralgia, the pain occurring after the initiation of hormone therapy and being described by the patients as different from those of rheumatoid

arthritis. The presence of radiological changes shows that the degenerative changes started before the initiation of oncological treatments and even the diagnosis of the neoplasm. It is possible that the hormone therapy caused the acceleration of degenerative changes and the occurrence of joint symptoms.

The risk of fracture in patients with breast cancer and endocrine therapy is increased compared to the general population. Thus, it is necessary for these patients to undergo the bone densitometry test and to correct their risk factors.

In addition to the clinical, biological and imaging evaluation of the patients, the QOLQ score was also applied to be able to evaluate the patient's opinion. This aspect is essential to increase the quality of life and adherence to the oncological treatment. The questionnaire was applied at the first assessment of the patient and after the treatment. At the first assessment, there were 48 patients who had mild-moderate impairment, 24 patients had moderate-severe impairment and 4 patients had severe impairment. After treatment, the QOLQ score was applied again, with 67 patients having mild-moderate impairment and 9 patients having moderate-severe impairment. This aspect highlights that the patient considered that the symptomatology improved after the rheumatology consultation, investigations and treatment.

There are many factors that may contribute to the occurrence of musculoskeletal manifestations after adjuvant hormone therapy of ER-positive breast cancer. An increased BMI is a risk factor both for the occurrence of breast cancer in menopausal women and for the occurrence of joint pain.

1.5 Conclusions

Following the adjuvant hormone therapy for the breast cancer with the presence of estrogen receptors, many rheumatological manifestations occurred. Arthralgia is among the most common side effect of these therapies, so there is a major interest in its identification and treatment.

In this study, patients with musculoskeletal manifestations were evaluated clinically, biologically and radiologically. Inflammatory joint diseases were excluded. Possible risk factors for the occurrence of musculoskeletal pain were evaluated, including smoking, BMI, stage of breast cancer, chemotherapy, radiotherapy and type of hormone therapy. There was a statistically significant correlation between overweight patients and cancer (Chi-square = 13.03, p=0.001).

Most of the patients who underwent chemotherapy (28) had DRUJ and MCP joint arthritis. Among the patients who underwent radiotherapy, most (13) had pain in the small joints of the hands.

The quality of life was the most affected in the case of patients with polyarthralgia and pain in the small joints of the hands. After the treatment, there were no patients with severe impairment.

The patients were treated according to the current recommendations, but also according to the experience of the rheumatologist. After the treatment, the musculoskeletal symptoms decreased or disappeared. There were no patients who stopped the hormone therapy prescribed by the oncologist.

Physicians should present possible adverse events and the importance of compliance to treatment before initiating hormone therapy. Patients should consult a rheumatologist for the assessment of joint pain and risk of fracture. Lifestyle changes, management of comorbidities, and treatment of adverse events should also be considered.

2. Study on musculoskeletal adverse events in immunotherapy patients

2.1 Introduction

The number of patients diagnosed with neoplasms is increasing, and the treatments are more numerous and more effective than in the past. Along with the evolution of this medical specialty, a new field appears, rather little studied, namely adverse events after cancer treatments.

Immunotherapy is a major innovation of cancer therapies, which has developed significantly in recent years. These therapies are continuously developing and being approved for the use in other types of cancer. Immune checkpoint inhibitors are monoclonal antibodies that activate the immune system to achieve a strengthening of antitumor immunity. But, acting on these control points, which have an important role in maintaining immune homeostasis, complications will occur. The immunological adverse events are very varied and can affect any organ, but the most common are dermatitis, diarrhea, colitis, endocrinopathy, neuropathy and pneumonitis.

Rheumatic immune-related adverse events have been described in numerous reports, but rheumatologists have limited experience in diagnosing and treating these new manifestations, so there is a need for training and guidelines for this new area of rheumatology. Diagnostic and treatment guidelines have been published, such as the 2017 European Society for Medical Oncology. Subsequently, three other agreements emerged, namely that of the Society for Cancer Immunotherapy, the American Society for Clinical Oncology, and the National Comprehensive Cancer Network. In 2020, the European Alliance of Associations for

Rheumatology published a guide for the diagnosis and treatment of rheumatic immune-related adverse events after immunotherapy.

Rheumatological toxicities of immunotherapy are reported more and more frequently. If the incidence of non-rheumatological adverse events is well known, the incidence of musculoskeletal manifestations is not precise, on the one hand because oncologists do not recognize them, they are underreported in clinical trials due to the non-recognition of symptoms by doctors or by patients. Oncological studies have a grading of adverse events from 1-5, from mild to life-threatening manifestations, but they do not distinguish the variety of rheumatological manifestations.

2.2 Materials and methods

The retrospective cohort study included 37 patients and took place over a period of 3 years, between 2019-2022 [11]. This study was carried out in the Rheumatology and Internal Medicine Clinic of "I. Cantacuzino" Hospital, with the approval of the Ethics Committee of the hospital, respecting the international norms for conducting research (ethical principles according to the Declaration of Helsinki).

The patients included in the study were treated with nivolumab, atezolizumab or pembrolizumab. Oncologists initially evaluated them. Patients who had joint pain, morning sickness, non-traumatic arthritis, muscle pain, muscle weakness, or new xerostomia/xerophthalmia after the administration of immunotherapy were referred to the rheumatologist for evaluation.

The differential diagnosis of musculoskeletal pain during immunotherapy is complex and must take into account degenerative joint changes, bone metastases and paraneoplastic syndromes.

Laboratory analyzes were collected to highlight the inflammatory syndrome, blood sedimentation rate (ESR) and C-reactive protein (CRP), which are altered in inflammatory arthritis, polymyalgia rheumatica or myositis. The evolution of the inflammatory syndrome should be followed to observe the response to the treatment of immune adverse events. Muscle enzymes, such as creatinine kinase (CK) and lactate dehydrogenase (LDH), were sampled from patients with muscle pain to highlight myositis. Antibodies, rheumatoid factor (RF) and antinuclear antibodies (ANA) were also sampled. Patients with muscle pain and increases in muscle enzymes had their myositis-specific antibody profile performed.

Afterwards, the imaging examination was performed: gray scale ultrasound and Doppler ultrasound to highlight synovitis, tenosynovitis, bursitis or enthesitis. Patients with

joint pain had X-rays performed at the level of the painful area. Imaging is important for the detailed description of the type of injury, but also for the investigation of alternative diagnoses. Electromyography (EMG) was recommended to patients suspected of myositis.

The severity of adverse events was assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, 2017. Grading is done out from 1 to 5 depending on the intensity of the manifestations.

2.3. Results

Incidence of musculoskeletal adverse events

In this study, there were 2 groups: the first of 37 patients, who had musculoskeletal adverse events after the administration of immunotherapy, and a control group of 312 patients, who were treated with immunotherapy, but had no rheumatological adverse events. Moreover, in this study, 37 patients with musculoskeletal manifestations were identified out of a total of 349 patients, so the incidence of rheumatological adverse events was 10.6%.

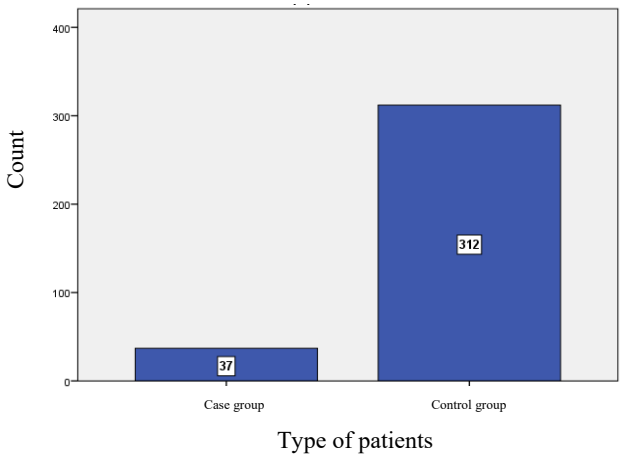

Fig. 2.1 Incidence of musculoskeletal adverse events

Age and gender of patients

Of the 37 evaluated patients, 24 were men, a percentage of 64.9%, and 13 were women.

Fig. 2.2 shows the analysis of the average age between the case-control groups. The mean age for the case group was 60.62 years (SD=8.00), and for the control group, the mean age was 64.41 years (SD=8.00).

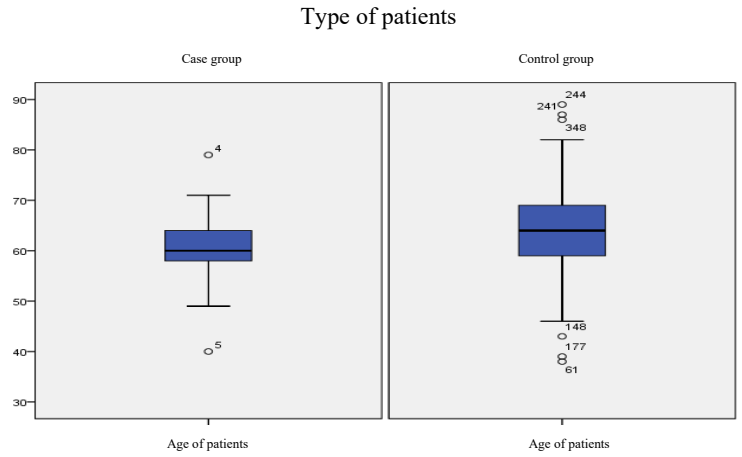

Fig. 2.2 Distribution of patients according to mean age in the case-control groups

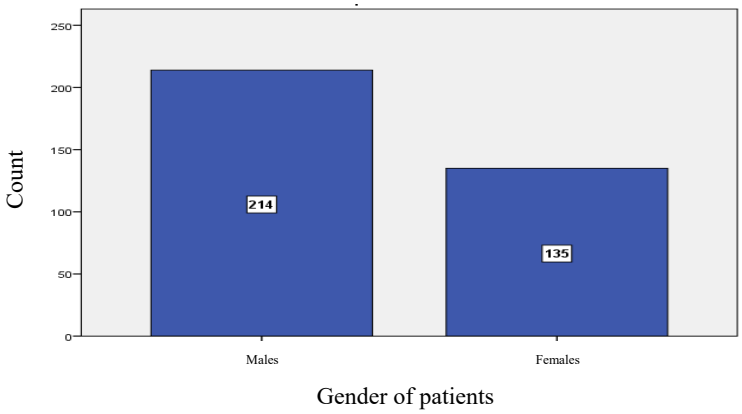

Fig. 2.3 Distribution of patients according to gender

Fig. 2.3 shows that there were more male patients (64.86%) compared to female patients (35.14%).

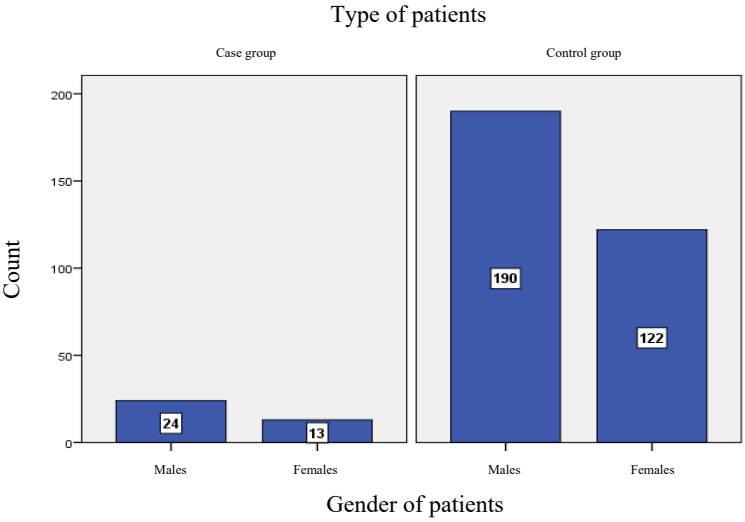

Fig. 2.4 Gender distribution of patients according to membership group

Similar to the case group, there were more male patients than female patients in the control group.

Smoking

Fig. 2.5 shows that 51.35% of the patients were smokers, and 48.65% were non-smokers.

There was a statistically significant correlation between the cancer type and smoking status (Chi-square = 24.03, p=0.001). Thus, smokers had non-small cell lung cancer (11) and urothelial carcinoma (4).

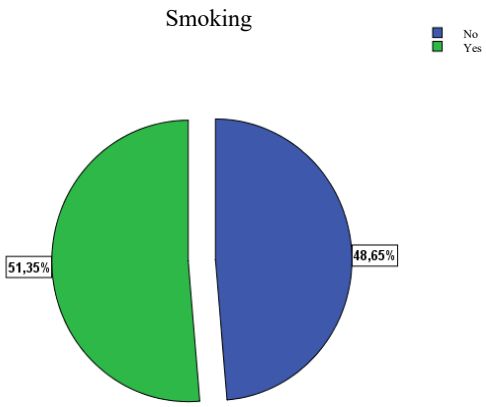

Fig. 2.5 Distribution of patients according to smoking

Type of cancer

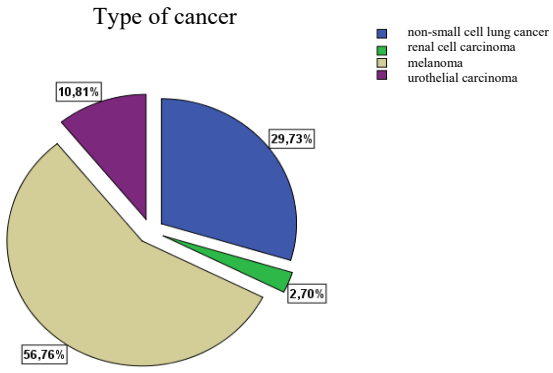

Fig. 2.6 Distribution of patients according to the type of cancer

In the group of 37 patients, most were diagnosed with melanoma (56.7%), 11 (29.7%) with non-small cell lung cancer, 4 (10.4%) with urothelial carcinoma and only one patient with renal cell carcinoma (2.7%).

There was a statistically significant difference between the case and control groups regarding the type of neoplasm (Chi-square = 26.40, p=0.001). Thus, melanoma was

predominant in the case group (21 versus 72), and renal cell carcinoma was predominant in the control group (49 versus 1).

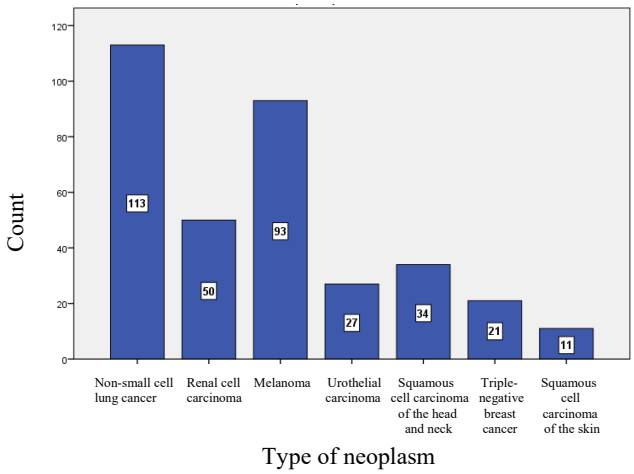

Fig. 2.7 Distribution of patients in the control group according to the type of neoplasm

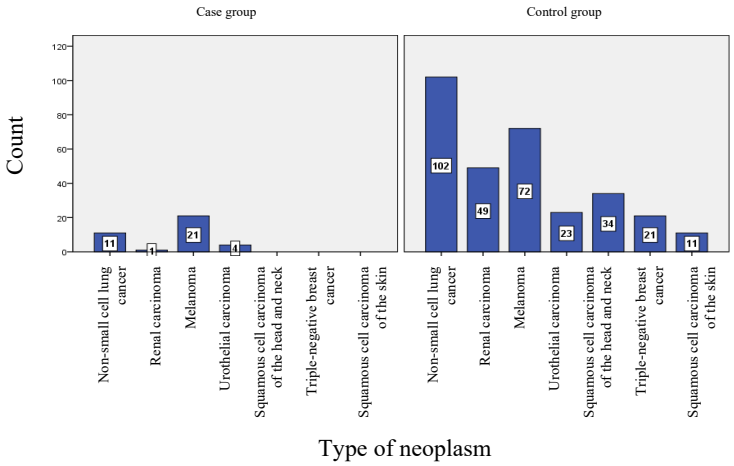

Fig. 2.8 Distribution of the neoplasm type according to the membership groups

Type of immunotherapy

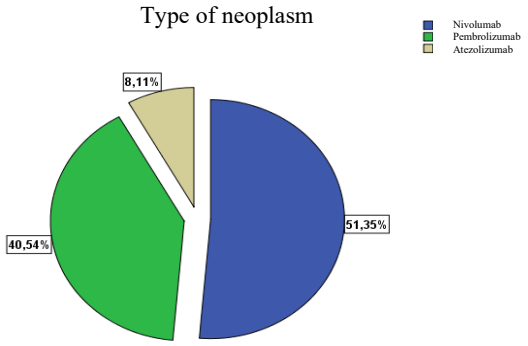

Fig. 2.9 Distribution of patients according to the type of immunotherapy

According to fig. 2.9, most of the patients were treated with anti-PD-1 antibodies, so there were 19 patients treated with Nivolumab (51.35%) and 15 patients treated with Pembrolizumab (40.54%). Only 3 patients were treated with anti PD-L1 antibodies, atezolizumab (8.11%).

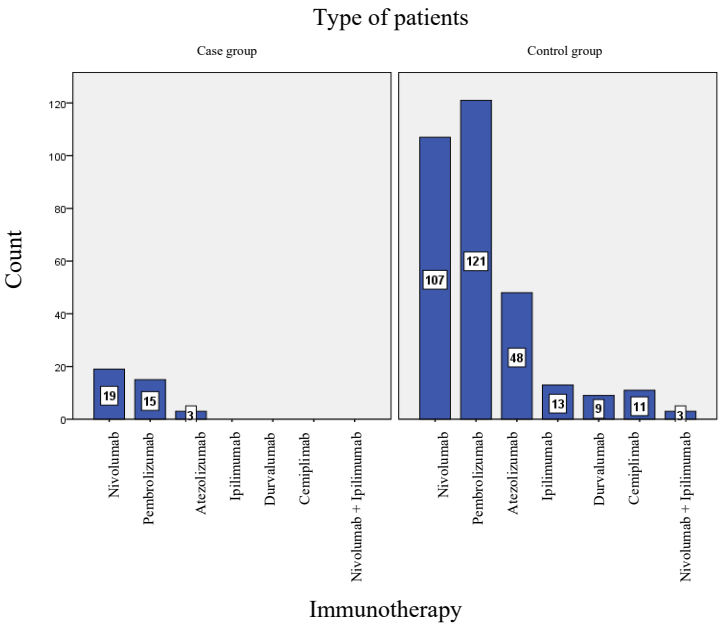

Fig. 2.10 The distribution of immunotherapy according to the membership groups

Fig. 2.10 shows the distribution of immunotherapy according to the membership groups. Although the difference in immunotherapy drug administration was not statistically significant, the most common drugs in the case group were Nivolumab (19) and Pembrolizumab (15), compared to the control group, in which the predominant medication was Pembrolizumab (121) and Nivolumab (107), along with other drugs such as Ipilimumab (13), Duralumab (9) and Cemiplimab (11).

Musculoskeletal adverse events

Rheumatological adverse events after administration of immunotherapy were varied, from arthralgia, myalgia, arthritis, bursitis, xerostomia and even rheumatoid arthritis [12].

Arthralgia and inflammatory arthritis

There was a statistically significant correlation between renal cell carcinoma patients and polyarthralgia (Chi-square = 37.00, p=0.001). Thus, one patient had a neoplasm of renal cell carcinoma type and had adverse events, polyarthralgia.

- **Knee pain**

10 patients with knee pain were identified, 5 of them being treated with nivolumab, and another 5 with pembrolizumab. After performing the ultrasound, enthesopathy was identified in most of the patients at the insertion of the quadriceps tendon on the patella and at the insertion of the patellar tendon on the tibial tuberosity.

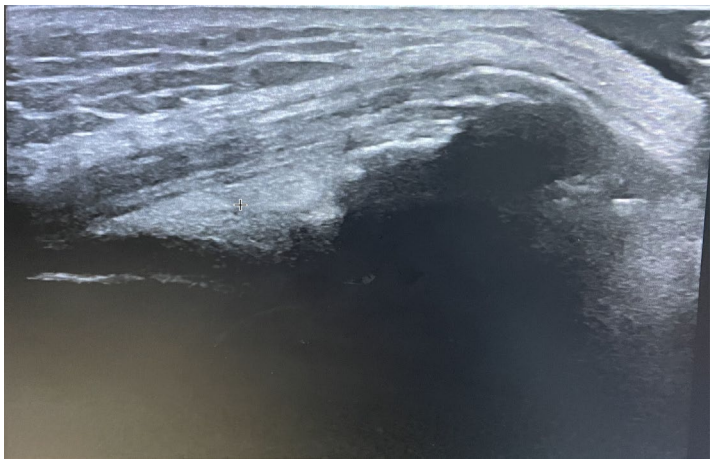

Fig. 2.11 Ultrasound image of a patient with patellar enthesopathy

Fig. 2.11 shows an ultrasound image of the knee in gray scale. The presence of calcifications at the insertion of the quadriceps tendon on the patella can be observed.

According to fig. 2.12, 27.03% of the patients had knee pain.

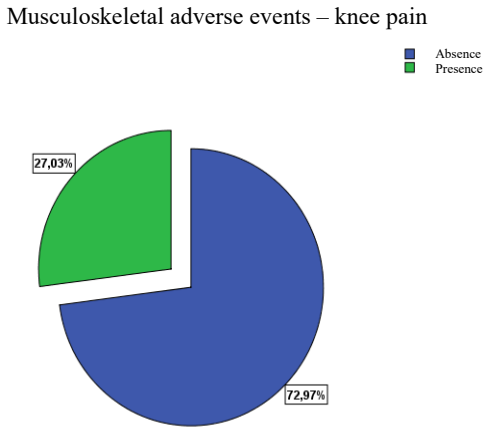

Fig. 2.12 Distribution of patients according to the presence of knee pain

- **Knee arthritis**

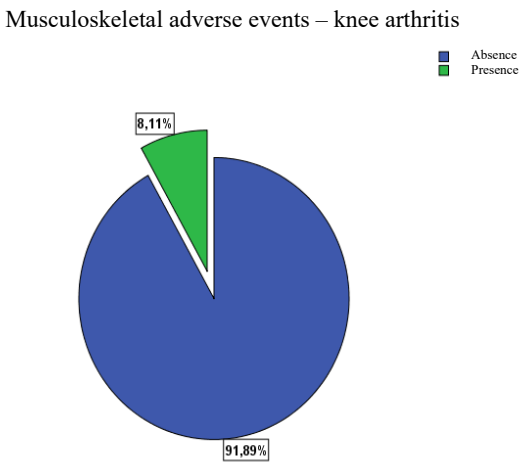

Fig. 2.13 Distribution of patients according to the presence of knee arthritis

3 patients had unilateral knee arthritis. Two of the patients were treated with nivolumab, and one patient was treated with pembrolizumab.

- **Arthralgia of the small joints of the hands**

5 patients had bilateral arthralgia of the small joints of the hands. Three of the patients were treated with pembrolizumab, one patient was treated with nivolumab and one with atezolizumab.

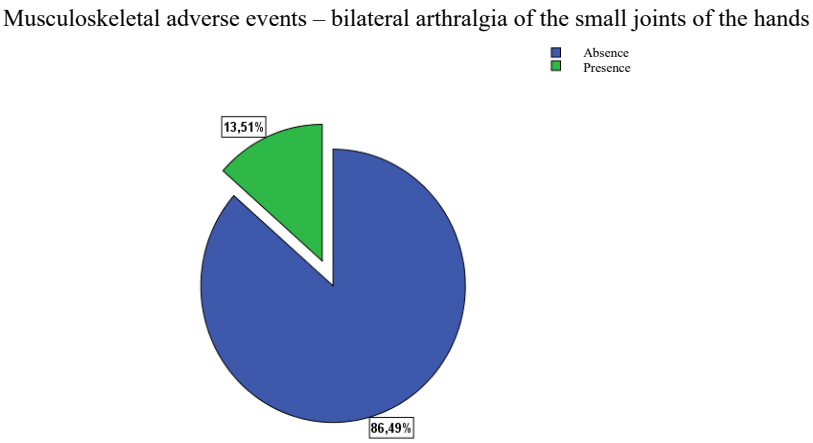

Fig. 2.14 Distribution of patients according to the presence of arthralgia of the small joints of the hands

There was a statistically significant correlation between the type of urothelial neoplasm and musculoskeletal adverse events, such as arthralgia of the small joints of the hands (Chi-square = 14.65, p=0.002).

- **Rheumatoid arthritis**

According to the 2010 American College of Rheumatology criteria, a 61-year-old smoker with non-small cell lung cancer on pembrolizumab was diagnosed with seropositive rheumatoid arthritis.

Prednisone 15 mg/day and sulfasalazine up to 2 g/day were started with the discontinuation of cancer treatment.

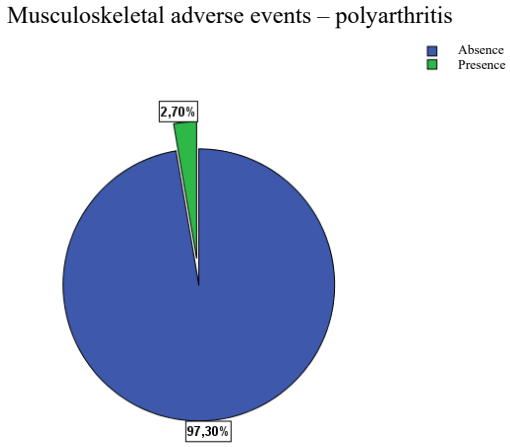

Fig. 2.15 Distribution of patients according to the presence of polyarthritis

- **Distal Radioulnar Joint (DRUJ) Arthritis**

5 patients with distal radioulnar joint arthritis were identified.

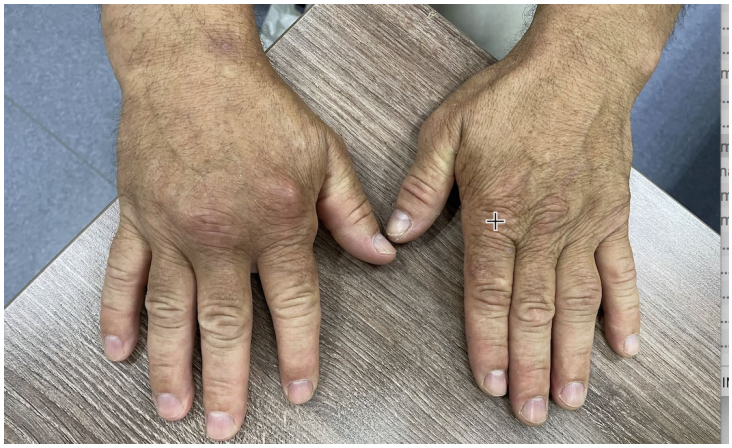

Fig. 2.16 Patient with right II-III distal radioulnar joint and metacarpophalangeal joint arthritis

Fig. 2.16 presents the upper limbs of a patient with swelling of the right II-III DRUJ and MCP joint.

There was a statistically significant correlation between the presence of atezolizumab immunotherapy and the DRUJ arthritis type adverse event (Chi-square = 4.85, p=0.02). Thus, 2 patients had adverse events of DRUJ arthritis type after immunotherapy with atezolizumab.

According to fig. 2.17, 18.92% of patients had DRUJ arthritis.

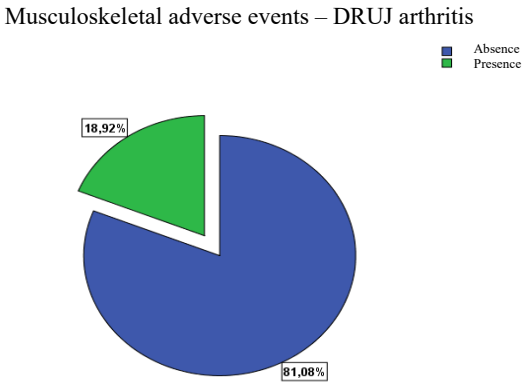

Fig. 2.17 Distribution of patients according to the presence of DRUJ arthritis

- **Osteoarthritis of the elbow and shoulder**

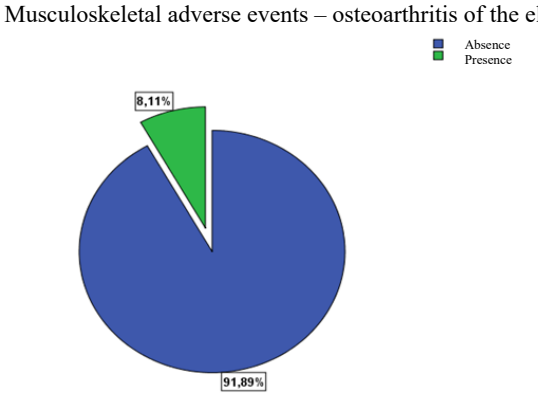

Fig. 2.18 Distribution of patients according to osteoarthritis of the elbow and shoulder

Fig. 2.18 shows that 8.11% of the patients had osteoarthritis of the elbow and shoulder.

- **Tibiotarsal joint pain**

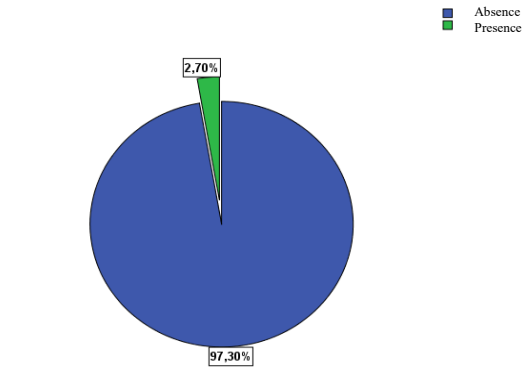

Fig. 2.19 Distribution of patients according to tibiotarsal joint pain

According to fig. 2.19, 2.7% of patients had tibiotarsal joint pain.

Myalgia

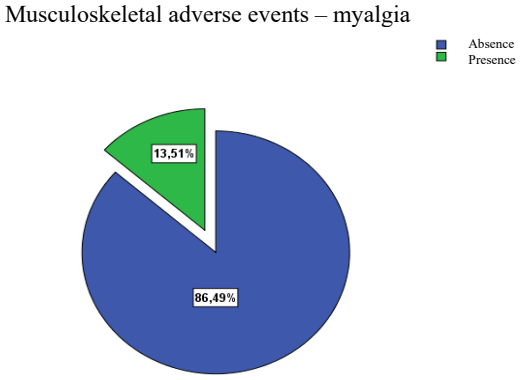

Fig. 2.20 Distribution of patients according to the presence of myalgia

According to fig. 2.20, 13.51% of the patients had myalgia.

Polymyalgia rheumatica and polymyalgia rheumatica-like syndrome

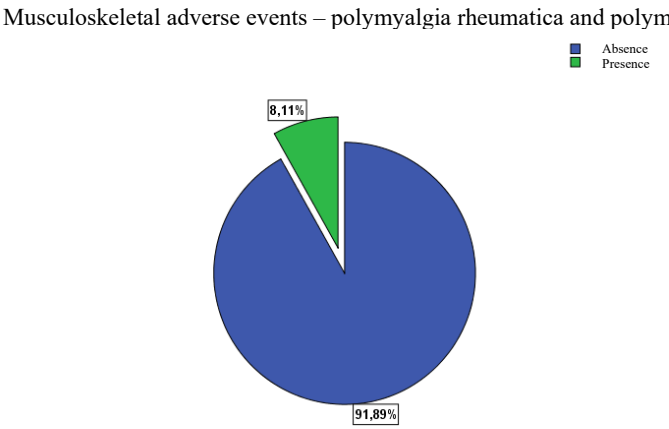

Fig. 2.21 Distribution of patients according to the presence of polymyalgia rheumatica and polymyalgia rheumatica-like syndrome

Fig. 2.21 shows that 8.11% of the patients had polymyalgia rheumatica.

Only one patient met the 2012 ACR/EULAR provisional criteria for the diagnosis of polymyalgia rheumatica.

There was a significant statistical difference regarding the gender between patients with biceps tendinopathy (Chi-square = 3.90, p=0.04). Thus, there was a significant statistical difference between males and females regarding the presence of biceps tendinopathy (0 versus 2).

Sicca Syndrome/ Sjogren Syndrome

According to the 2016 American-European Consensus Criteria, one patient was diagnosed with Sjogren's syndrome. Patients were treated with NSAIDs for arthralgia and artificial tears for ocular impairment. The joint symptomatology improved, thus immunotherapy discontinuation was not necessary.

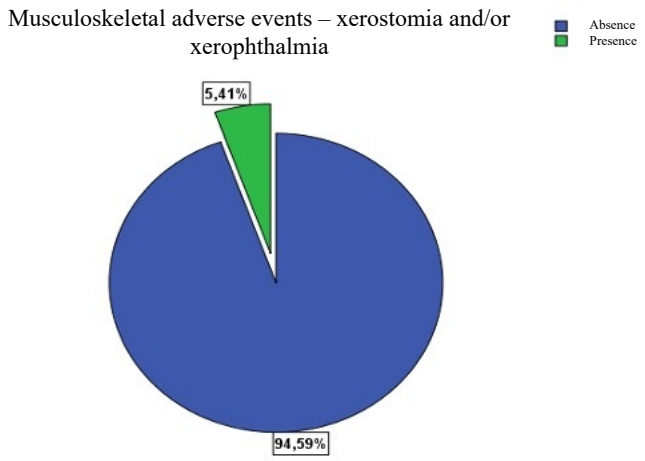

Fig. 2.22 Distribution of patients according to the presence of xerostomia, xerophthalmia

There was a statistically significant correlation between treatment with atezolizumab and the adverse events such as xerostomia and xerophthalmia (Chi-square = 4.98, p=0.02). Thus, one patient had Sicca syndrome following the administration of immunotherapy with atezolizumab.

Other immune adverse events

The control group was made up of 312 patients who did not present rheumatological adverse events, but had other immune toxicities. These are shown in table 2.1.

As it can be observed in table 2.1, many immune-related adverse events were identified in the control group after the administration of immunotherapy. The most frequent adverse events were skin reactions.

Although there is a small number of cases, the information can have a significant contribution and the results can be used in other pilot studies.

Table 2.1. Distribution of adverse events according to the type of immunotherapy in the control group

	Immunotherapy							
Type of adverse events	Nivolumab	Pembrolizumab	Atezolizumab	Ipilimumab	Durvalumab	Cemiplimab	Nivolumab+Ipilimumab	Total
musculoskeletal	19	15	3	0	0	0	0	37
hepatitis and hepatic cytolysis	10	13	8	0	0	0	1	32
skin	30	53	15	6	2	4	0	110
endocrinological	8	13	4	0	0	0	2	27
diarrhea	14	17	7	2	1	0	0	41
colitis	2	4	1	0	1	0	0	8
pneumonitis	1	3	0	0	0	0	0	4
neurological	3	1	0	0	0	0	0	4
Total	87	119	38	8	4	4	3	263

The most frequent adverse events identified in the control group were skin, digestive, endocrinological, neurological, pulmonary manifestations. There were patients who had other adverse events besides the rheumatological ones.

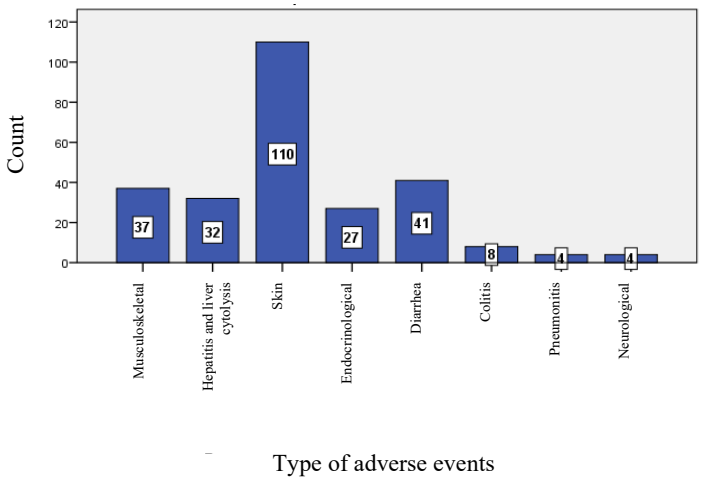

Fig. 2.23 Distribution of patients according to the type of adverse events

Serology

All 37 patients had the following sampled: rheumatoid factor (RF), anti-nuclear antibodies (ANA), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). Lactate dehydrogenase (LDH), creatine kinase (CK) and myositis antibody profile were sampled from patients with muscle pain.

Anti-nuclear antibodies

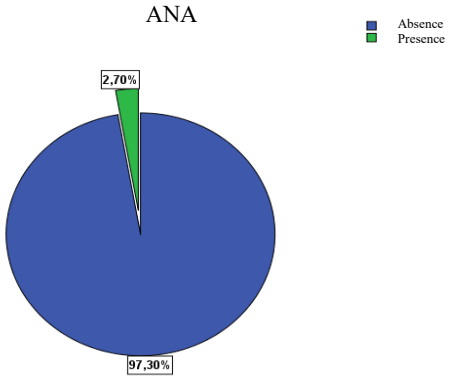

Fig. 2.24 Distribution of patients according to the presence of ANA

Fig. 2.24 shows that 2.7% of the patients had a positive ANA.

Anti-nuclear antibodies were sampled from all the patients. Only in the case of one patient did they have a slightly increased titer, and when the extended profile was performed, anti-Ro antibodies were present.

This patient had Sicca syndrome and DRUJ arthritis and was diagnosed with Sjogren Syndrome.

Presence of the inflammatory syndrome

CRP was elevated in 56.76% of cases, and ESR was elevated in 54.05% of cases.

The mean value of CRP analysis for the 37 patients was 8.47 (± 13.28).

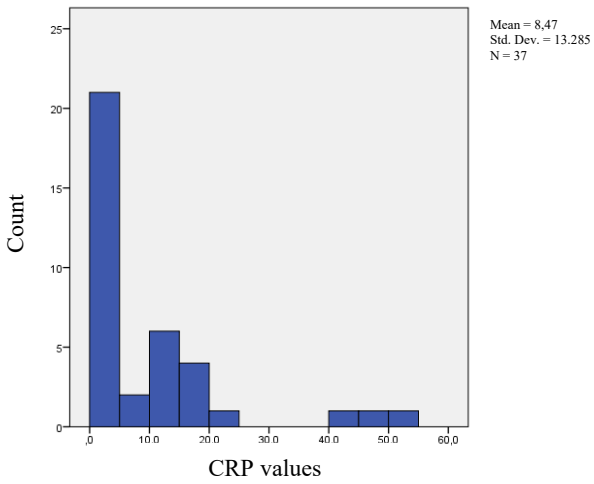

Fig. 2.25 Quantitative distribution of CRP

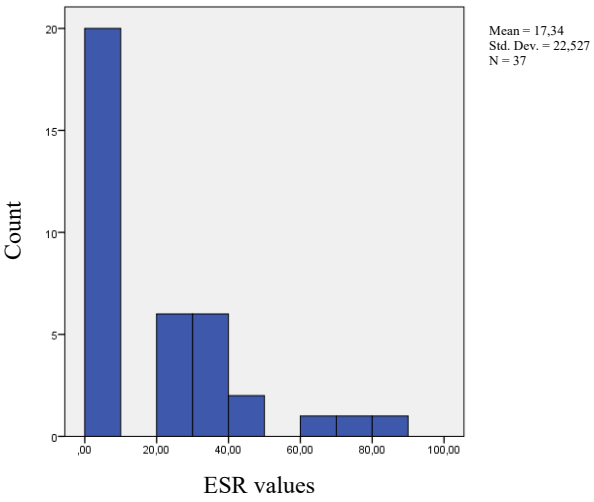

Fig. 2.26 Quantitative distribution of ESR

The mean value of the ESR analysis for the 37 patients was 17.34 (± 22.52).

Degree of musculoskeletal adverse events

There were 22 patients with grade 1 adverse events, 10 patients with grade 2 adverse events, and 5 patients with grade 3 adverse events. Regarding patients with severe adverse events, 4 were males, 3 being treated with nivolumab and 2 with pembrolizumab. Immune-related adverse events started between 4 and 16 weeks after the initiation of immunotherapy. It should be noted that the patient who had symptoms after 16 weeks received a double dose of pembrolizumab.

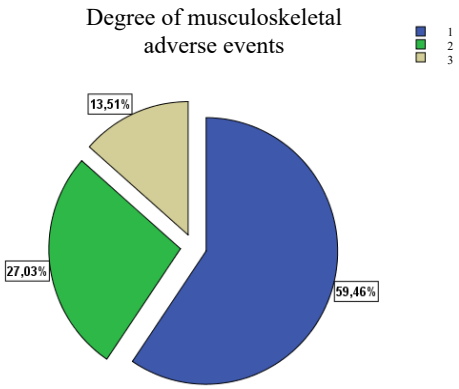

Fig. 2.27 Distribution of patients according to the degree of musculoskeletal adverse events

Fig. 2.27 shows the distribution of patients according to the degree of adverse events. Thus, most patients (59.46%) had grade 1 toxicity. 27.03% of the patients had grade 2 toxicity and 13.53% had grade 3 toxicity.

The time elapsed from the initiation of immunotherapy until the onset of adverse events

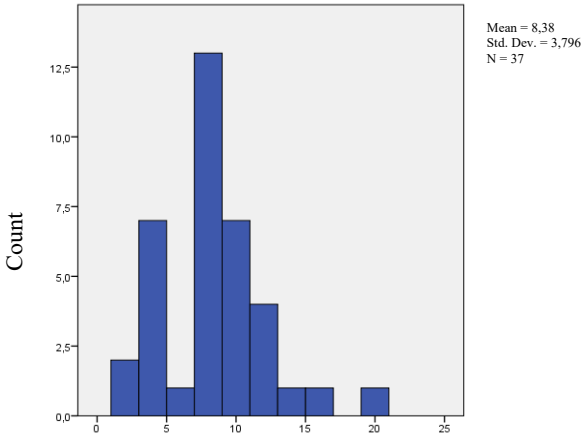

Fig. 2.28 Distribution of patients according to the time elapsed from the initiation of immunotherapy to the onset of musculoskeletal adverse events

The mean value at the onset of adverse events was 8.38 (± 3.79).

Treatment of rheumatic immune-related adverse events

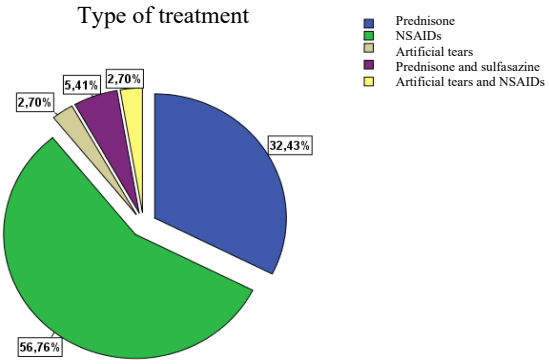

Fig. 2.29 Distribution of patients according to the type of treatment administered

As observed in fig. 2.29, most of the patients (56.76%) received oral and topical NSAIDs treatment. Immunotherapy discontinuation was not necessary in these patients.

The second most common treatment administered was prednisone, in an average dose of 10-20 mg/day. These patients had grade 2 and 3 rheumatological toxicities. The patients who received 10 mg of prednisone continued immunotherapy, and those who received 15 mg and 20 mg, respectively, discontinued the oncological treatment until the remission of symptoms.

Treatment with sulfasalazine was started in 2 of the patients with grade 3 rheumatological adverse events.

In this study, no patients required biological treatment (anti-TNF-alpha antibodies [14]).

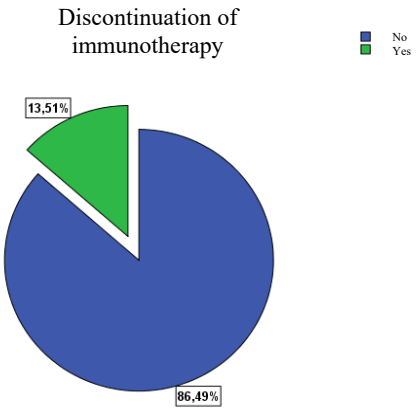

Fig. 2.30 Distribution of patients according to discontinuation of immunotherapy

As shown in fig. 2.30, 13.51% of the patients discontinued immunotherapy. In the case of the other patients (86.49%), discontinuation of immunotherapy was not necessary.

Oncological treatment was discontinued in 5 of the patients, those who had a prednisone dose of 15-20 mg/day.

Associated diseases

Autoimmune diseases

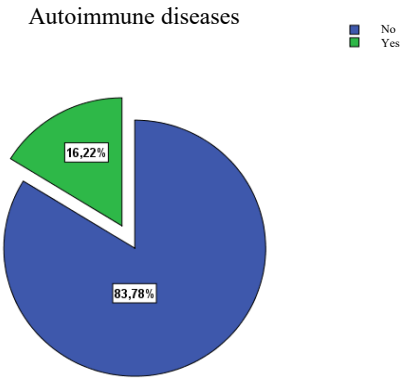

Fig. 2.31 Distribution of patients according to the presence of associated autoimmune diseases

Fig. 2.31 shows the distribution of patients according to the presence of autoimmune diseases, thus 16.22% of the patients had associated autoimmune diseases.

Fig. 2.32 shows the distribution of patients according to the association with autoimmune diseases. Thus, 6 patients had autoimmune diseases before the initiation of immunotherapy, 4 of them being previously diagnosed with Hashimoto's thyroiditis (10.81%) and 2 patients with vitiligo (5.41%). In this study, no patients with rheumatic autoimmune diseases were observed before the initiation of the oncological treatment.

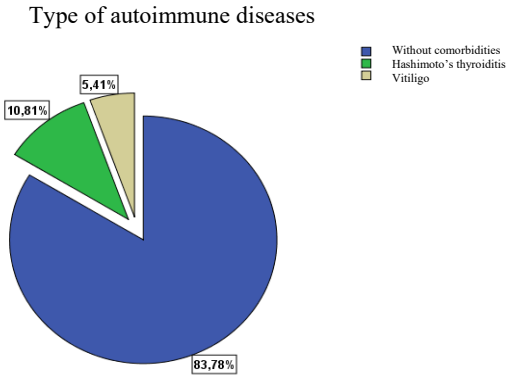

Fig. 2.32 Distribution of patients according to the association with other autoimmune diseases

Hyperuricemia

Fig. 2.33 shows the distribution of patients according to hyperuricemia, thus 7.14% showed elevated levels of uric acid in the blood.

4 patients had hyperuricemia without signs of inflammatory arthritis. All these patients were being treated with allopurinol and had normal uric acid levels at the time of examination.

There was a statistically significant correlation between the type of neoplasm and the type of comorbidity - hyperuricemia (Chi-square = 14.08, p=0.002). Thus, patients with hyperuricemia had renal cell carcinoma.

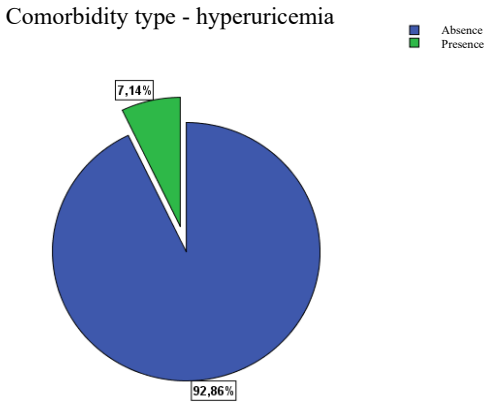

Fig. 2.33 Distribution of patients according to the presence of hyperuricemia

Obesity

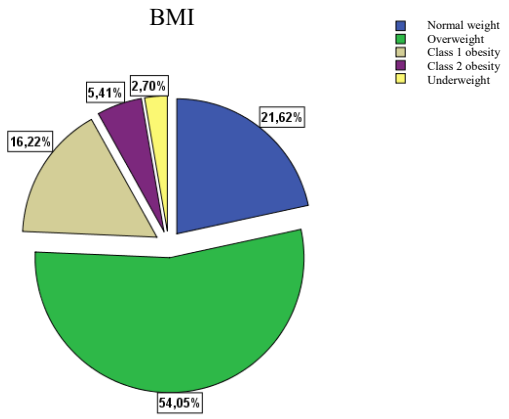

Fig. 2.34 Distribution of patients according to BMI

According to fig. 2.34, in this study, 21.62% normal weight patients were included, 54.06% were overweight, 16.22% had class 1 obesity, 5.41% had class 2 obesity and 2.7% were underweight.

There was a statistically significant correlation between the patients' BMI and the adverse event of knee pain (Chi-square = 9.49, p=0.05). Thus, patients who suffered from class 2 obesity had knee pain.

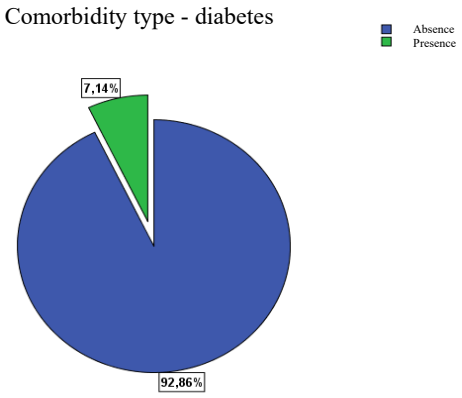

Fig. 2.35 Distribution of patients according to the presence of diabetes

Fig. 2.35 shows the distribution of patients according to the presence of diabetes. Thus, 7.14% of the patients had type 2 diabetes. All the patients were treated with oral antidiabetic agents.

2.4 Discussions

Rheumatological adverse events occurring after the administration of immunotherapy are increasingly common, considering the permanent increase in the number of patients treated with these drugs. Most of the time, the musculoskeletal manifestations are mild or moderate,

but they need to be diagnosed and treated as early as possible, in order not to affect the quality of life of the patients, but also to improve compliance to the oncological treatment.

Musculoskeletal manifestations were varied: arthralgia, arthritis, polymyalgia rheumatica, rheumatoid arthritis, Sicca and Sjogren syndrome.

Patients with mild adverse events were treated with topical and oral NSAIDs, if they were not contraindicated. Patients presenting with arthralgia responded favorably to this treatment. In the case of patients with moderate adverse events, the administration of prednisone in medium doses was necessary. Most patients responded well to corticotherapy, with a few exceptions in which symptoms recurred when the doses were reduced. In these cases, the lowest dose of prednisone was maintained for a longer period of time. There were also some severe adverse events, in which corticosteroid therapy was not sufficient and background regimen with sulfasalazine was added.

The decision to continue or discontinue immunotherapy after the onset of immune-related adverse events is made according to the severity of the symptoms. In the case of mild adverse events, the therapy is maintained, in the case of moderate ones, it is discontinued until the remission or improvement of the symptoms, and in the case of life-threatening manifestations, immunotherapy will be permanently discontinued.

Although oncologists try to reduce the incidence and assess the risk of immune-related adverse events, these measures are not enough. Collaboration with rheumatologists is necessary to correctly diagnose and treat these patients. On the other hand, immune-related adverse events must be correctly differentiated from other musculoskeletal pathologies, including bone or soft tissue metastases and even paraneoplastic syndromes.

There is concern that immunomodulatory/immunosuppressive treatment could affect tumor response to immunotherapy leading to tumor progression [13]. However, at present, there is not enough data to be able to analyze the impact that the immunosuppressive treatment has on the evolution of the neoplasm.

There are also limitations of this study. First, the small number of patients with musculoskeletal adverse events was recorded. Immunotherapy is a new treatment, and the number of patients who have benefited from this therapy has been limited. In the future, the indications of the treatments will expand, which will lead to a much larger number of patients treated with immunotherapy. On the other hand, both oncologists and patients tend not to report joint pain. This happens both due to the limited time of oncologists, who omit to examine the patients musculoskeletal, but also to the fact that the patients usually have many symptoms, so they will neglect the musculoskeletal pain. Another problem encountered was the difficulty of

following these patients over a longer period. All the patients in this study had metastatic cancer, having numerous complications related to the oncological disease, so that consultations with the rheumatologist, as well as their compliance to the treatment, were quite difficult.

2.5 Conclusions

The most common rheumatological manifestations after immunotherapy were arthralgia, inflammatory arthritis and polymyalgia rheumatica. Most of the patients had mild and moderate symptoms.

The response of patients with musculoskeletal immune-related adverse events to NSAIDs and corticosteroid treatment was encouraging. Few patients required the addition of background regimens.

Patients with musculoskeletal adverse events were treated by rheumatologists according to existing recommendations for these rheumatological manifestations. However, more extensive studies are needed to have a correct guide for diagnosis and treatment, taking into account that immune-related adverse events do not comply with the classical forms of rheumatological diseases.

The aim of this study was to correctly diagnose and treat, as early as possible, patients with rheumatological adverse events after the administration of immunotherapy. It is important for the patient to be able to continue the oncological treatment and obtain the targeted antitumor response.

At present, more studies are needed regarding the mechanisms of action of immunotherapy in order to obtain the desired antitumor response, at the same time diminishing immune-related adverse events.

3. Conclusions and personal contributions

Conclusions

The first part of this PhD thesis presents important elements about the history of immunotherapy and cancer immunology. This information is essential for the understanding of the mechanism by which immune-related adverse events occur after the use of immune checkpoint inhibitors. In the next chapter from the general part, information related to estrogen, selective estrogen receptor modulators (tamoxifen) and aromatase inhibitors is detailed. By understanding how these treatments work, patients can be helped to manage side effects.

In the special part, the patients who had rheumatological adverse events after the administration of oncological treatments were examined. They were evaluated clinically, biologically and radiologically, later a rheumatological diagnosis was made and the appropriate treatment was initiated. In addition to trying to highlight the most frequent musculoskeletal toxicities that can occur after neoplastic treatments, an attempt was made to emphasize the risk factors that can lead to the onset of these manifestations. Aiming at all these aspects, the prevention of musculoskeletal side effects or the early initiation of adequate treatment will be attempted.

The special part of the PhD thesis presented two studies. The first study included 76 postmenopausal women with estrogen receptor-positive breast cancer who had musculoskeletal symptoms after taking estrogen inhibitors, and the second study included 349 patients who were treated with immunotherapy. Of these, 37 had rheumatological adverse events.

In the first study, women diagnosed with invasive ductal carcinoma or invasive lobular carcinoma with the presence of hormone receptors were included. The 76 evaluated patients had stage 1, 2 and 3 invasive carcinomas. They received adjuvant treatment with letrozole, anastrozole, exemestane or tamoxifen. Among the 76 patients, 5 had a history of seropositive rheumatoid arthritis before the oncological diagnosis. All 5 patients had background regimen for rheumatoid arthritis, being in remission.

1. There was a statistically significant correlation between overweight patients and cancer (Chi-square = 13.03, p=0.001).
2. There was a statistically significant correlation between the different cancer types and DXA scores (Chi-square = 33.23, p=0.001). Thus, there was a correlation between the presence of osteopenia and stage 2 cancer and osteoporosis and stage 3 cancer.
3. There was a statistically significant correlation regarding the stage of the cancer and the type of hormone therapy administered (Chi-square = 19.43, p=0.003). Thus, in the case of stage 1 cancer, the patients followed hormone therapy with letrozole, anastrozole and exemestane, in the case of stage 2 cancer, the patients followed hormone therapy similar to stage 1 cancer and in addition with tamoxifen, and in stage 3 cancer, the patients had hormone therapies with letrozole and anastrozole.
4. The most frequent clinical articular manifestations after endocrine adjuvant therapy of breast cancer were DRUJ and MCP joint arthritis, followed by patients with polyarthralgia, then gonalgia, coxalgia, the fewest patients presenting pain in the scapulohumeral joints.

5. The most frequent adverse events occurred after treatment with letrozole, followed by patients treated with anastrozole, exemestane and tamoxifen.
6. Most patients with DRUJ and MCP joint arthritis were smokers, as were those with gonalgia, polyarthralgia and scapulohumeral periarthritis.
7. The onset of clinical manifestations was on average 3 months after the initiation of adjuvant hormone therapy.
8. Most of the patients who underwent chemotherapy had DRUJ and MCP joint arthritis, followed by patients with polyarthralgia, gonalgia, coxalgia and scapulohumeral periarthritis.
9. Among the patients who underwent radiotherapy, most had DRUJ and MCP joint arthritis, then polyarthralgia, gonalgia and coxalgia.
10. 36 patients were diagnosed with arthritis of the hands and 25 with gonarthrosis. 4 patients were diagnosed with carpal tunnel syndrome, 3 with bilateral subscapularis calcific tendonitis, 2 patients with extensor tenosynovitis, and 2 patients had vertebral compression.
11. The 5 patients with a history of seropositive rheumatoid arthritis had new polyarticular joint pain, especially gonalgia, after starting the treatment with aromatase inhibitors.
12. The QOLQ score was applied at the first assessment. 48 patients had mild-moderate impairment, 24 had moderate-severe impairment and 4 had severe impairment. After the treatment, the QOLQ score was applied again (on average 1 month after the first patient assessment), and 67 patients had mild-moderate impairment and 9 moderate-severe impairment.
13. 22 patients were diagnosed with osteoporosis, of which 8 were on bisphosphonate treatment at the time of evaluation. 31 patients had osteopenia and 23 had normal values of bone densitometry. Bisphosphonate treatment was recommended both to patients with osteoporosis and to those who had osteopenia due to the increased risk of fracture.
14. Depending on the symptoms and the diagnosis, treatment with NSAIDs, vitamin D3, bisphosphonate, chondroprotectors and omega 3 fatty acids was initiated. The disruption of hormone therapy was not necessary in any patient.
15. The exact cause of the musculoskeletal manifestations could not be specified, even if they started after the initiation of hormone therapy. Given that the study was retrospective, patients could miss the exact time of the onset of symptoms. Postmenopausal women may experience symptoms similar to side effects of aromatase inhibitors or tamoxifen. A control group of patients, without adjuvant therapy, would have been necessary to observe the incidence of rheumatological manifestations.

16. The differential diagnosis of musculoskeletal symptoms that started during immunotherapy was complex and had to consider degenerative joint changes, bone metastases and paraneoplastic syndromes. Paraneoplastic syndromes can manifest as inflammatory rheumatological diseases, the most common being seronegative arthritis, hypertrophic osteoarthropathy, polychondritis, erythema nodosum, inflammatory myositis and paraneoplastic eosinophilic fasciitis.

17. Most of the patients in the study (64.9%) were men. The mean age was 60.62 years.

18. There was a statistically significant difference between the case and control groups regarding the type of neoplasm (Chi-square = 26.40, p=0.001). Thus, melanoma was predominant in the neoplasm group (21 versus 72), and renal cell carcinoma was predominant in the control group (49 versus 1).

19. Most of the patients were treated with anti-PD-1 antibodies (Nivolumab), followed by patients who were treated with pembrolizumab and those with atezolizumab.

20. Rheumatological adverse events after the administration of immunotherapy varied from arthralgia, myalgia, arthritis, bursitis, xerostomia, to rheumatoid arthritis.

21. There was a statistically significant correlation between renal cell carcinoma patients and polyarthralgia (Chi-square = 37.00, p=0.001). Thus, one patient had a neoplasm of renal cell carcinoma type and had polyarthralgia as an adverse event.

22. There was a statistically significant gender difference between patients with biceps tendinitis (Chi-square = 3.90, p=0.04). Thus, a statistically significant difference between male and female patients resulted from the presence of biceps tendinitis (0 versus 2).

23. There was a statistically significant correlation between treatment with atezolizumab and adverse events such as xerostomia and xerophthalmia (Chi-square = 4.98, p=0.02). Thus, one patient had Sicca syndrome following the administration of atezolizumab immunotherapy.

24. 22 patients had grade 1 adverse events, 10 patients had grade 2 adverse events and 5 patients had grade 3 adverse events.

25. Immune-related adverse events started between 4 and 16 weeks after the initiation of immunotherapy. Severe adverse events occurred after the administration of nivolumab and pembrolizumab.

26. Most of the patients were treated with oral and topical NSAIDs. Disruption of immunotherapy was not necessary in these patients. All patients treated with NSAIDs had grade 1 adverse events, arthralgia or myalgia.

27. The second most common treatment administered in an average dose of 10-20 mg/day was prednisone. These patients had grade 2 and 3 rheumatological toxicities. Patients who received 10 mg of prednisone continued immunotherapy and those who received 15 mg and 20 mg, respectively, discontinued the oncological treatment until symptom remission.
28. Sulfasalazine treatment was initiated in 2 of the patients with grade 3 rheumatological adverse events. One of the patients was diagnosed with rheumatoid arthritis and the second had distal radioulnar joint arthritis. These patients were treated concomitantly with prednisone and the oncological treatment was discontinued. The patient diagnosed with rheumatoid arthritis did not resume immunotherapy due to joint symptoms, but also due to the fact that he did not respond to the oncological treatment, having significant tumor progression.
In this study, no patients required biological treatment (anti-TNF-alpha antibodies).
29. 6 patients had autoimmune diseases before the initiation of immunotherapy, 4 of them being diagnosed with Hashimoto's thyroiditis and 2 with vitiligo. In this study, no patients had rheumatic autoimmune diseases before the initiation of the oncological treatment.

Personal contributions

A problem encountered was the difficulty of following these patients over a longer period. All the patients in this study had a metastatic neoplasm and many complications related to the oncological disease, so that consultations with the rheumatologist and the compliance to treatment were quite difficult.

The study limitations included the small numbers of patients and the low ethnic and racial diversity. Studies that evaluate a larger number of patients are needed, so as to identify more variables that can influence the rheumatological manifestations, which occur after oncological treatments.

Although there is a limited number of cases, the information can be a significant informative contribution and the results can be used in other pilot studies.

The results of these studies have shown that the toxicities of oncological treatments are a real problem. To identify patients with adverse events, standardized questionnaires for toxicities should be available in oncology clinics. Given the high volume of patients, a lot of members of the medical staff in the oncology clinic are not available to investigate mild or moderate adverse events.

At present, there is no guide for the diagnosis and treatment of musculoskeletal adverse events after oncological treatments. The toxicities that occur after hormone therapy are generally similar to the symptoms that start post menopause.

However, toxicities after immunotherapy represent a new group of rheumatological conditions. These syndromes are similar to rheumatic diseases, but do not meet known diagnostic criteria. The onset of symptoms can be unpredictable, just like the evolution and response to treatment.

References

1. Lipitz-Snyderman A, Pfister D, Classen D, Atoria CL, Killen A, Epstein AS, Anderson C, Fortier E, Weingart SN. Preventable and mitigable adverse events in cancer care: Measuring risk and harm across the continuum. *Cancer*, 123(23):4728-4736, 2017 Dec 1. doi: 10.1002/cncr.30916. Epub 2017 Aug 17. PMID: 28817180; PMCID: PMC7539686.
2. Bai RL, Chen NF, Li LY, Cui JW. A brand new era of cancer immunotherapy: breakthroughs and challenges. *Chin Med J (Engl)*, 134(11):1267-1275, 2021 May 19. doi: 10.1097/CM9.0000000000001490. PMID: 34039862; PMCID: PMC8183825.
3. **Cretu I**, Bojinca M, Milicescu M, Cretu B, Ionescu R. Immune checkpoint inhibitors and rheumatic adverse events. Ro J Rheumatol, XXVII(4), 2018. DOI: 10.37897/RJR.2018.4.1.
4. Lumachi F, Luisetto G, Basso SM, Basso U, Brunello A, Camozzi V. Endocrine therapy of breast cancer. *Curr Med Chem*, 18(4):513-22, 2011. doi: 10.2174/092986711794480177. PMID: 21143113.
5. Groom AG, Younis T. Endocrine therapy for breast cancer prevention in high-risk women: clinical and economic considerations. *Expert Rev Pharmacoecon Outcomes Res*, 16(2):245-55, 2016. doi: 10.1586/14737167.2016.1159514. Epub 2016 Mar 17. PMID: 26923683.
6. Jordan VC, Robinson SP. Species-specific pharmacology of antiestrogens: role of metabolism. *Fed Proc*, 46(5):1870-4, 1987 Apr. PMID: 3556610.
7. Geisler J, King N, Anker G et al. In vivo inhibition of aromatization by exemestane, a novel irreversible aromatase inhibitor, in postmenopausal breast cancer patients. *Clin Cancer Res*, 4:2089-2093, 1998.
8. Di Giacomo AM, Calabrò L, Danielli R, Fonsatti E, Bertocci E, Pesce I, et al. Long-term survival and immunological parameters in metastatic melanoma patients who responded to ipilimumab 10 mg/kg within an expanded access programme. *Cancer Immunol Immunother*, 62:1021-28, 2013.
9. Ferrucci PF, Ascierto PA, Pigozzo J, Del Vecchio M, Maio M, Antonini Cappellini GC, et al. Baseline neutrophils and derived neutrophil-to-lymphocyte ratio: prognostic relevance in metastatic melanoma patients receiving ipilimumab. *Ann Oncol*, 27:732-38, 2016.

10. Simeone E, Gentilcore G, Giannarelli D, Grimaldi AM, Caracò C, Curvietto M, et al. Immunological and biological changes during ipilimumab treatment and their potential correlation with clinical response and survival in patients with advanced melanoma. *Cancer Immunol Immunother*, 63:675-83, 2014.
11. **Cretu I**, Cretu B, Cirstoiu C, Cursaru A, Milicescu M, Bojinca M, Ionescu R. Rheumatological Adverse Events Following Immunotherapy for Cancer. *Medicina (Kaunas)*, 58(1):94, 2022 Jan 8. doi: 10.3390/medicina58010094. PMID: 35056402; PMCID: PMC8778975.
12. **Creţu I**, Bojincă M, Milicescu M, Cursaru A, Șerban B, Crețu B, Iordache S, Pop CS, Cîrstoiu C, Ionescu R. Musculoskeletal adverse reactions after immunotherapy for cancer: A case series. *Exp Ther Med*, 22(3):1027, 2021 Sep. doi: 10.3892/etm.2021.10459. Epub 2021 Jul 16. PMID: 34373713; PMCID: PMC8343871.
13. Horvat TZ, Adel NG, Dang TO, Momtaz P, Postow MA, Callahan MK, et al. Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at Memorial Sloan Kettering Cancer Center. *J Clin Oncol*, 33:3193-8, 2015.
14. **Cretu I**, Geoanta C, Bogheanu O, et al. Cerebral Tuberculosis in a Patient Following Treatment With Infliximab for Ankylosing Spondylitis: A Case Report. *Cureus*. May 17, 2023; 15(5): e39117. doi:10.7759/cureus.39117.

Published papers:

1. **Cretu I**, Cretu B, Cirstoiu C, Cursaru A, Milicescu M, Bojinca M, Ionescu R. Rheumatological Adverse Events Following Immunotherapy for Cancer. Medicina (Kaunas). 2022 Jan 8;58(1):94. doi: 10.3390/medicina58010094. PMID: 35056402; PMCID: PMC8778975. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8778975/
2. **Creţu I**, Bojincă M, Milicescu M, Cursaru A, Șerban B, Crețu B, Iordache S, Pop CS, Cîrstoiu C, Ionescu R. Musculoskeletal adverse reactions after immunotherapy for cancer: A case series. Exp Ther Med. 2021 Sep;22(3):1027. doi: 10.3892/etm.2021.10459. Epub 2021 Jul 16. PMID: 34373713; PMCID: PMC8343871. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8343871/
3. **Ioana Cretu**, Mihai Bojinca, Mihaela Milicescu, Bogdan Cretu, Ruxandra Ionescu. Immune checkpoint inhibitors and rheumatic adverse events Ro J Rheumatol. 2018;XXVII(4). DOI: 10.37897/RJR.2018.4.1. AMPH - RJR_2018_4_Art-01 - Page 1 (publitas.com)
4. **Cretu I**, Geoanta C, Bogheanu O, et al. Cerebral Tuberculosis in a Patient Following Treatment With Infliximab for Ankylosing Spondylitis: A Case Report. Cureus. May 17, 2023; 15(5): e39117. doi:10.7759/cureus.39117. https://www.cureus.com/articles/156141-cerebral-tuberculosis-in-a-patient-following-treatment-with-infliximab-for-ankylosing-spondylitis-a-case-report#!/authors