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Problems of palliative care in patients with multiple myeloma

Abstract

Background. In cases of multiple myeloma, palliative care includes patients who still undergo active oncological treatment and those who have discontinued it. The aim of the research is to present the difficulties which doctors of palliative care and others taking care of patients with multiple myeloma may face.

Material and methods. The trial included patients of home hospice care and the patients of a Palliative Care Ward. Retrospective analysis based on medical documentation was applied and, in patients that were still on treatment, prospective observation was conducted.

Results. The analysis included four patients on chemotherapy and two patients for whom intensive oncological treatment had been discontinued. The most frequent symptoms were afflictions connected to bone pain. These were often accompanied by secondary neurological symptoms of pathological bone fractures or compressions caused directly by the neoplastic tumour and symptoms of peripheral neuropathy. Secondary nephropathy (myelomic kidney) and a tendency to hypercalcaemia occurred. Various symptoms of blood hyperviscosity syndrome (dysfunctions of organs: kidneys, heart; bleeding gums and nose) were observed. Additionally during palliative care, it was essential to notice and counteract disease aggravations.

Conclusion. Patients with multiple myeloma constitute a great challenge in palliative care due to the changeable clinical course of the disease, repetitive relapses and remissions. Numerous symptoms of the disease require continuous observation and the proper treatment, which demonstrates that simultaneous multi-specialist care is essential.

Key words: multiple myeloma (plasmocytoma), palliative care, chemotherapy, rehabilitation

Introduction

Plasmocytoma (multiple myeloma) belongs to a group of diseases called monoclonal gammopathy. It is a neoplasm of B lymphocytes. It is characterized by the proliferation of atopic plasmocytes, most often in flat and long bones that produce monoclonal immunoglobulin: M-protein (class IgG 55%, IgA 30%). The urine of patients often contains immunoglobulin light chains (Bence-Jones protein). Plasmocytoma is a disease of the haematogenic system and it constitutes ~1% of all neoplasms and ~13 % of the neoplasms of the haematogenic system [1–6].

The symptoms of multiple myeloma are connected to the development of neoplastic cells and the activity of cytokines and the proteins they produce. The patients suffer from many different afflictions in the course of the disease. The most frequent symptom is bone pain (60% of cases). This mainly concerns the spine, flat bones (pelvis, ribs, skull) and long bones. The pain is caused by osteolytic changes and the pathological fractures (compressive vertebral fractures or pathological fractures of long bones). Secondary to bone deformations, neurological symptoms may appear as a result of spinal cord compression, spinal nerve root compression or cra-

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nial nerve compression. These symptoms may also be caused by the direct compression of nerve structures by a neoplastic tumour. In the case of very advanced changes, paresis or paralysis of limbs may be observed. As far as neurological ailments are concerned, we may observe symptoms of peripheral neuropathy, usually of the mixed type (sensorimotor). The symptoms are usually a result of demyelination and degeneration of nerve fibres, neoplastic invasion, amyloidosis (in the neighbourhood of nerves or vessels responsible for vascularization of nerves), and of the direct toxic influence of M-protein on nerve endings, which takes place in blood hyperviscosity syndrome.

Patients with multiple myeloma often suffer from chronic renal disease. At the moment of diagnosis, the problem already concerns 30% of the patients. Light chains are deposited in the kidneys and form amyloid. Amyloid damages the kidneys and prompt interstitial inflammatory lesions. Interstitial nephritis may also be induced by the deposition of calcium concrements in the renal tubules, and both hypercalcaemia and hypercalciuria are observed in some patients.

Secondary amyloidosis and hyperuricaemia with the precipitation of uric acid crystals may appear in the collecting tubules. Hypercalcaemia results from hyperactivity of osteoclasts and its symptoms may be discrete and may develop slowly. The symptoms include drowsiness, headache, orientation disorders, nausea, vomiting, constipation, asthenia or muscular adinamia, dysphagia, polyuria, and dehydration [1–3, 6, 7].

Deterioration in the functioning of the immunological system stems from the presence of improper immunoglobines, which favours infections, especially of the respiratory and urinary systems. The risk of infection is further increased during and after chemotherapy. In about 10% of patients with multiple myeloma, hyperviscosity syndrome, connected to the increased concentration of M-protein, is observed. This mostly concerns IgA multiple myeloma because it is mainly immunoglobulin A that polymerizes and closes microcirculatory vessels, which may contribute to a deterioration in the functions of many organs. It is a cause of symptoms from the central nervous system: drowsiness, consciousness disturbances, hearing deterioration, and headaches. Coagulation disorders cause bleeding, especially from the nose and gums.

In 80% of cases with multiple myeloma, the patients suffer from anaemia, which is caused by the disease itself or as a secondary effect of chemotherapy (myelosuppressive treatment).

The dysfunction of organs is called CRAB:

- C (calcium) — increased concentration of calcium >10 mg/dl;
- R (renal) — concentration of creatinine > 2 mg/dl;
- A (anaemia) — Hgb < 10 g/dl;
- B (bone) — osteolysis [1, 2, 4].

Multiple myeloma may be in the shape of a single plasmocytoma tumour and appear mainly in the bones (4%). Only in 1–2% of cases is it located elsewhere in the body [1, 5, 6]. Plasma cell leukaemia is usually but not always seen in advanced disease, constituting around 4% of plasmocytoma. It is diagnosed on the basis of improper plasmocytes in the blood. The prognosis for the disease is pessimistic, the course is rapid and the disease is usually accompanied by hepato- and splenomegalia and lymphadenopathy [1, 6].

Aim

The aim of this study was to present the difficulties that specialists in palliative medicine and others taking care of patients with multiple myeloma may face. We also wanted to draw attention to the diversity of symptoms and a selection of the secondary complications that often need to be investigated by many specialists, thus demonstrating that the treatment should be multi-dimensional.

Material and methods

The Bioethics Committee of the Collegium Medicum in Bydgoszcz, gave consent to conduct the trial. The analysis included patients with multiple myeloma who, between 2006 and 2007 were treated by specialist in palliative medicine either in Palliative Care Department of University Hospital or in home care provided by the Priest Jerzy Popiełuszko Hospice in Bydgoszcz. Retrospective analysis based on the medical documentation completed during diagnostics, haematological treatment and palliative care was used. In the cases of patients who were alive during the trial, prospective observation was conducted. The analysis included information about the diagnosis, haematological treatment that had been introduced or withdrawn, symptoms of the disease and any clinical difficulties connected with them.

Results

The trial included six patients (Table 1). Five of them had died before the commencement of the trial and one of them is still being treated by

Table 1. Characteristics of patients

Patient (sex, age)	Coexistent diseases	Bone pain	Administered painkillers	Bisphosphonate	Clinical problem
Patient 1 (M, 81)	Hypertension Secondary myocardiopathy with mitral and aortal incompetence Oesophagogastritis Liver cyst Kidney cysts Bilateral cataract	Yes Condition after compressive fracture of L2 vertebral body Osteoarthritis	Paracetamol Tramadol	Yes	Mucous membrane bleeding Anaemia
Patient 2 (M, 74)	Hypertension A condition after heart attack	Yes Condition after compressive fracture of Th 8	Paracetamol NSAIDs Tramadol	Yes	Throat pain Anaemia Ion disorders
Patient 3 (F, 67)	Hypertension Nodular goitre during hypothyreosis Chronic endogastritis A condition after cholecystectomy	Yes Condition after compressive fracture of Th12 and L3 Discopathy of L4 and L5 A condition after left-side fracture of ribs	Paracetamol NSAIDs Tramadol	Yes	Upper airways infections Otolaryngological infections Anaemia
Patient 4 (M, 67)	Chronic renal disease Condition after left orchidectomy because of cancer	Yes Numerous osteolytic changes in the course of the disease	Paracetamol Tramadol	Yes	LE paresis Muscular atrophy Anaemia
Patient 5 (M, 67)	(-)	Yes Osteoarthritis of spinal kolumn	Paracetamol NSAIDs Tramadol	Yes	Anaemia Subfebrile conditions Sweating
Patient 6 (F, 70)	Diabetes type 2 Chronic renal disease Hypertensional myocardiopathy during cardiac failure II NYHA Condition after engraftment of right hip joint endoprothesis Condition after BSOH	Yes Condition after compressive fracture of Th 4 and 5 Condition after pathological fracture of right radial bone	Paracetamol NSAIDs Tramadol Morphine	Yes	LE paresis Anaemia Chronic renal disease

M — male; F — female; NSAIDs — non-steroidal anti-inflammatory drugs; NYHA — New York Heart Association; LE — lower extremities; BSOH — bilateral salpingectomy, oophorectomy and hysterectomy

a haematologist and provided with home palliative care.

Patient 1

Patient (M): 81 years old, diagnosed with multiple myeloma in November 2006. Preliminary diagnostics revealed compressive fracture of the vertebral body of L2, proliferation of plasmatic cells in bone marrow, aleukocytosis, secondary anaemia and chronic oesophagogastritis. The patient was referred to the Haematology Department and intravenous infusion of disodium pamidronate was given because of hypercalcaemia. Due to agranulocytosis, the patient was administered filgrastim, recombinant human granulocyte-colony stimulating factor (G-CSF). Back pain decreased and the patient was advised to wear a Jewett-type corset. In 2007, chemotherapy according to the scheme of MP (melphalan, prednizone) was introduced. Following chemotherapy (ChTH), the patient was hos-

pitalized because of bilateral pneumonia. In March 2007, ChTH was continued and the patient was provided with home hospice care due to periodical chronic spinal pain. Each time the patient was on the Haematology Ward, he received a transfusion of packed red blood cells (PRBC) and, once, he was administered with G-CSF due to agranulocytosis. He also suffered from bleeding from the left nose wing and the mucous membranes of the mouth. Those incidents led to severe anaemia and required the transfusion of PRBC and constant administration of etamsylate. In June 2007 a colonoscopy performed after the bleeding from the lower gastrointestinal tract showed a few diverticula of the sigmoid colon and a polyp which was then removed. The orthopaedic surgeon advised gradual discontinuation of the Jawett corset and in the case of an aggravation of the afflictions he suggested preparing a lumbar corset with laces for the patient. During home care, a haematologist was regularly con-

sulted in order to establish further proceedings. During the following periods of hospitalization, a progression of secondary nephropathy was observed in the patient: increasing concentration of creatinine from 1.2 mg/dl on the day of diagnosis to 2 mg/dl (05.2007) and finally 5.5 mg/dl during the last stay in hospital in July 2007. Then, due to significant anaemia (Hgb 5.2 g/dl), PRBC transfusion was conducted. When the patient returned home, repetitive bleeding from the mucous membranes of the nose and rectal bleeding were observed. The patient died at home on 5 August 2007. The direct cause of death was probably related to the severe secondary anaemia.

Patient 2

Patient (M): 74 years old with multiple myeloma IgG type kappa diagnosed seven years ago. Medical history included a compressive fracture of the thoracic spine at Th8, secondary nephropathy, bilateral disseminated flat and nodular solid lesions in chest connected to the parietal pleura. Previously the patient had been treated with subsequent cycles of chemotherapy, however in November 2006, the VMCP scheme (vincristine, melphalan, cyclophosphamide and prednisone) was introduced, but did not result in disease remission. The patient underwent transfusion of leucocyte-poor irradiated PRBC because of secondary anaemia and a plasmapheresis was conducted twice due to a high level of monoclonal protein. The patient was qualified for further treatment with cytostatics according to the VAD scheme (vincristine, doxorubicin and dexamethasone). After July 2007, he was referred to home palliative care due to bone pain and progressive asthenia. In August 2007, the patient was admitted to the Haematology Ward in order to continue chemotherapy. Due to strong retrosternal pain and dyspnoea, he was referred to the Cardiology Ward and the coronarography and a percutaneous angioplasty of the right coronary artery were performed. At that time, probably after contrast administration, a deterioration of chronic renal disease was observed. The creatinine level increased from 1.3 mg/dl to 2.9 mg/dl (on discharge: 1.57 mg/dl). After returning home, the patient complained of pains in the stomach, chest and knee joints which were moderately controlled by tramadol and ketoprofen. The condition of the patient gradually deteriorated, he accepted meals with difficulty, and the amount of liquids he was drinking lowered significantly. In September 2007, a control examination showed an increase in the creati-

nine level to 3.49 mg/dl and electrolyte disorders (potassium 5.64 mmol/l, sodium 119 mmol/l). Regardless of intravenous treatment, no clinical improvement was achieved. The patient died in September 2007 at home, probably due to advanced disease and chronic renal failure.

Patient 3

Patient (F): 67 years old with multiple myeloma IgG type kappa, diagnosed in March 2006. Before diagnosis was confirmed, she had been treated with percutaneous vertebroplasty of Th12 with bone cement because of a compressive fracture of Th12 and L3 vertebrae. That treatment significantly diminished the pain. In April 2006 the diagnosis confirmed multiple myeloma (total protein 13.46 g/dl, monoclonal protein 8.67 g/dl, plasmocytes in the marrow 74.4%, osteolysis in the skull and femoral bones) and the patient was qualified for cytostatic treatment (VAD scheme). The chemotherapy was complicated by bronchopneumonia in the course of neutropenia and superficial phlebitis of the left lower extremity. The patient needed a wide spectrum antibiotic, G-CSF and a transfusion of leucocyte-poor irradiated PRBC. Then the patient was referred to home palliative care because of bone pain resistant to NSAIDs. Tramadol in a dose of 3×50 mg provided the satisfactory pain relief and NSAIDs were stopped. The patient continued chemotherapy, first according to the VMCP scheme, then he received cyclophosphamide and dexamethason due to leucopenia. Following several cycles of chemotherapy patient was very weak and suffered from repetitive infections of the upper airways, the middle ear and conjunctivitis. In June 2007, the diagnosis showed a zoster located in the underarms, along the right costal margin. Additionally, the patient suffered from hearing deficit of the left ear which according to a laryngologist, was probably a result of the chemotherapy. Actually, apart from cytostatics administered systematically, the patient is treated with bisphosphonates (due to the bone lesions and hypercalcaemia) and tramadol in a dose of 3×50 mg orally with satisfactory pain relief.

Patient 4

Patient (M): 67 years old with multiple myeloma diagnosed in January 2007 with multiple osteolytic lesions. The patient was qualified for chemotherapy and he was administered with VI cycles according to the VAD scheme. In August 2007, he was referred for hospice home care due to pain. On admission the patient had sense disorders in both lower ex-

tremities with coexistent muscular atrophy, pains along the spine escalating during movement and features of cachexia. His medical history included left-side orchidectomy because of cancer in 1991 with subsequent chemo- and radiotherapy, and chronic renal disease and secondary anaemia. Due to pain symptoms (mainly bone pain), the patient was treated with tramadol, dexamethasone and bisphosphonates. In October 2007, the clinical condition of the patient suddenly deteriorated, the patient became weaker, with disturbed communication and difficulties in swallowing. The patient had died before the planned additional tests could be carried out (hypercalcaemia was suspected because of multiple osteolytic lesions).

Patient 5

Patient (M): 68 years old with multiple myeloma diagnosed in August 2004. At the time of diagnosis, monoclonal IgG lambda-type proteins were observed as well as an increased level of plasmocytes in the marrow. Bones radiographs did not show any osteolytic changes, which are typical for myeloma. The patient qualified for chemotherapy according to the VMCP scheme. In September 2004, during the II cycle of chemotherapy (VBAP — vincristine, carmustine, doxorubicin and prednisone), antiviral drugs were added to the treatment because of herpes. In March 2005, after three full changeable cycles, the patient was admitted to the Haematology Ward in order to assess the grade of development of the disease. A biopsy of the marrow from the sternum provided non-guttate contents, a non-diagnostic material. In May 2006 after trepanobiopsy of the marrow (hypoplastic marrow) and a myelogram (presence of 53.6% lymphoplasmatic cells and 4.8% plasmocytes) the patient was qualified for treatment according to the changeable scheme. Neutropaenia and an inflammation of the deep veins of the right leg complicated chemotherapy. In February 2007, another trepanobiopsy was conducted. It showed hypercellularity of the marrow, and myeloma infiltrations (CD38+) constituted around 90% of all cells in the represented fragment. The patient was treated with dexamethasone due to pancytopenia. After consultation in the Haematology Clinic of the Collegium Medicum in Gdańsk in May 2007, the patient was qualified for chemotherapy with thalidomide joined with dexamethasone infusions. Due to complications during the treatment (high fever with chills, *E.coli* bacteraemia, requiring targeted antibiotic therapy) the thalidomide treatment was discontinued. During the stay on the Haematology

Ward in July 2007, chemotherapy according to the MP scheme was introduced to the treatment. While being hospitalized during the course of the disease, the patient required several transfusions of PRBC due to primary anaemia, as well as the administration of filgrastimes due to neutropaenia. The patient often experienced heightened body temperature (mainly subfebrile states and also fever periodically) and sweating. During home care the patient exhibited a periodical exacerbation of spinal pain, so he was administered tramadol, NSAIDs and paracetamol (also due to abnormal body temperature and sweating). The patient died on 30 October 2007 in Hospice. The exact cause of death remains unknown.

Patient 6

Patient (F): 70 years old with multiple myeloma diagnosed in March 2005. She was qualified for chemotherapy according to the VMCP scheme and received the last cycle in April 2007. In May 2007, the patient was admitted to the Neurosurgical Ward of the University Hospital due to pathological spinal fracture (compressive fracture of Th 4 and 5) as a result of an injury. A computer tomography of the spine showed a pathological mass (59 × 39 mm), which filled a significant part of the spinal channel Th5–Th6, developing towards the chest, probably with descending aorta invasion. The patient was qualified for symptomatic treatment. Due to surrounding chest pain and paresis of the lower extremities, the patient was referred to the Palliative Care Ward on 15 May 2007. He also suffered from diabetes type 2, secondary nephropathy (on admission creatinine 2.3 mg/dl), secondary anaemia and hypertension myocardiopathy. On admission, the patient was initially administered tramadol. However, due to the unsatisfactory pain relief, tramadol was replaced by morphine which was gradually increased to a dose of 60mg per day. Due to deterioration and chronic renal disease (a rise of creatinine concentration to 3.9 mg/dl, hyperkalemia: potassium 6.7 mmol/l, and metabolic acidosis), the treatment was changed to subcutaneous administration of morphine and the intravenous antibiotic therapy which were adjusted to the level of renal failure. After hydration and intravenous infusions of glucose with insulin, the concentration of creatinine and potassium in the blood serum decreased. During her stay on the Palliative Care Ward, the patient demonstrated deterioration in chronic renal disease and in general clinical condition. The patient was provided with the support of a psychologist and



Figure 1. Osteolytic lesions in the course of multiple myeloma, right prearm bone (patient no. 6)

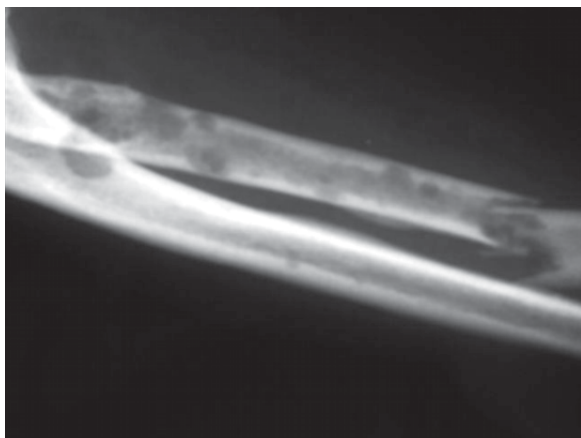


Figure 2. Pathological fracture of right radial bone (patient no. 6)

physiotherapist. The rehabilitation conducted on the ward included passive exercises of the lower limbs, active exercises of the upper limbs and breathing exercises. When the patient's condition deteriorated and muscle strength weakened, active exercises were supported passively and finally only passive exercise of the upper and lower limbs was carried out. During the stay on the Palliative Care Ward, the patient experienced a pathological fracture of the right radial bone (Figures 1 and 2). A plaster splint was applied after orthopaedic consultation. The patient died due to anaemia and renal failure.

Discussion

Patients with multiple myeloma require concise interdisciplinary cooperation during treatment. In many cases, patients undergoing palliative care are still treated with chemotherapy, which is connected

with frequent hospitalization and the necessity of cooperation between the haematologist and the palliative medicine specialist. The tasks of haematologists include choosing the proper course of treatment based on the results of additional tests and the patient's clinical condition. The palliative medicine specialist who takes care of a patient with multiple myeloma will often have to deal with the long-lasting complications of the treatment provided, as well as the symptoms of the primary disease and its secondary afflictions. Patients in this population suffer from bone pain, often caused by pathological fractures and their consequences (neurological disorders). That is why they are often referred for palliative care. At least 30% of such patients have features of chronic renal disease, which will also develop in a further 20–30%. As a result of osteolysis, patients with multiple myeloma often have abnormal plasma calcium values but hypercalcaemia may remain unnoticed for a long time. Anaemia and weakness are typical for almost all the patients. Doctors during palliative care may also encounter bleeding caused by hyperviscosity syndrome. The basic form of treatment for multiple myeloma is chemotherapy, which most often allows for the achievement of a stable decrease of plasmocytes in the marrow and of the concentration of M-protein in blood serum and urine. It also decreases osteolytic lesions. There are several schemes for cytostatic treatment provided in cases of myeloma. The schemes differ in respect to aggressiveness and the manner of drug administration. If remission of the disease occurs, long-lasting maintenance chemotherapy is conducted [2, 3, 5, 6]. All the patients described were provided with chemotherapy according to different schemes. In one case, thalidomide was administered after the cytostatics with which the patient had been treated earlier proved to be non-effective. The drug suppresses angiogenesis of the marrow microenvironment, induces apoptosis of myeloma cells, and suppresses secretion of factors that stimulate the development of neoplasm plasmocytes (IL-6, TNF). Thalidomide joined with dexamethasone (this combination is efficient in around 50% of patients) was administered to patient no. 5. Although in various tests the analysis of the drug's side-effects suggests it is safe, the patient experienced high fever with chills and the blood culture was positive for *E.coli* bacteria, which required targeted antibiotic therapy [2, 4, 6, 7].

Infections were also observed in other analysed patients. They took place either immediately after chemotherapy or about 2 weeks after the treatment,

when side-effects connected to the cardiovascular system normally occur (leucopenia, neutropaenia, granulocytopenia, anaemia, thrombocytopenia or even pancytopenia). They mostly concerned the respiratory system and the otolaryngological zone. Some patients required hospitalization. Patients with myeloma are characterized by a significant deterioration in immunity and, as a result, they are prone to infections. If such infections occur, treatment with antibiotics of a wide spectrum should always be considered and started early. If granulocytopenia is diagnosed, it may be necessary to use factors stimulating granulopoiesis [2, 3, 6].

The most frequent symptom in this group of patients is bone pain. It is estimated that it concerns 60–70% of patients. The pain is often acute, especially during movement and bone system ballasting. It is most often connected to existent pathological lesions in bones, being either a direct effect of the disease or its secondary result (pathological fractures). Treatment of pain in these patients is extremely difficult because it is associated with many constraints. Usually in cases of bone pain, the first choice drugs are NSAIDs. However, in patients with myeloma benefits of administration of NSAIDs should be carefully weighted against the risk of depressed glomerular filtration rate (GFR) in some cases leading to renal failure. If we include opioids in pain therapy, especially in cases of patients with myeloma and coexistent chronic renal disease, the dosage usually has to be adjusted to the level of renal failure. Most opioids used in therapy for chronic pain with deterioration of renal functions should either be administered in reduced dosages or the intervals between doses should be prolonged. In end-stage chronic renal disease, the maximum dose of tramadol should not exceed 50 mg twice a day [8]. In the case of morphine metabolized in the liver and discharged through the kidneys, active metabolites can accumulate in patients with renal failure. The dosage of the opioid, therefore, has to be modified according to GFR [9]. In this clinical case, it might be advisable to consider the administration of renally safer opioid, the elimination of which does not depend on the kidneys to a great extent (methadone, fentanyl or buprenorphine).

All the analysed patients were on NSAIDs. However, in the case of patient no. 1 the acetylsalicylic acid was administered as prophylaxis for myocardial infarction, not because of pain. When bleeding appeared, due to the coexistence of thrombocytopenia, the administration of the drug was discontinued. Non-steroidal anti-inflammatory drugs were ad-

ministered to patient no. 6 only at the beginning of hospital therapy and were rotated to opioids which led to the pain relief. In the case of patient no. 2, after stent implantation to the coronary artery acetylsalicylic acid (and clopidogrel) were ordered due to cardiological indications. In this case, a deterioration in renal functions took place immediately after the contrast had been administered during coronarography. We cannot exclude the negative influence of NSAIDs on accelerating the process of renal function deterioration. NSAIDs were administered occasionally to patient no. 5 with competent kidneys and patient no. 3 still takes them occasionally.

Bone pain can be successfully treated with radiotherapy and may be ameliorated by corticosteroids. Radiotherapy is also advisable in cases of weight bearing bones which are threatened with fracturing, especially around the spine, humerus and femoral bone. None of the patients underwent radiotherapy. Steroids, which might sometimes be helpful were administered only in the case of patient no. 4.

For a better quality of life, it is important that the patients remain physically active. Therefore, rehabilitation in this group is a significant supplement to the symptomatic treatment. It is essential that the strategies for activating the patients are adjusted to the particular phase of the disease and the direct and indirect aims of the activity are established. When constructing an activation programme we should foresee complications of the disease or its progress and we should act in order to minimize their implications [10, 11]. In rehabilitation of patients with multiple myeloma, attention should be paid especially to the necessity of stabilizing the bones by orthopaedic equipment as a prophylaxis for pathological fractures and protection against spinal fractures. Corsets, laces and stabilization belts should be used (as in the cases of patients no. 1 and no. 3). Stabilization of the spine has to be carefully considered when the patient is immobilized and physical activity is constrained. The risk of pathological fractures is quite low at such patients (no load on the movement system) and the stabilization itself disables the proper ventilation of the lungs which, along with the long-lasting immobility and often old age of the patients, significantly increases the risk of complications in the respiratory system. Stabilization in patients lying down may also contribute to life's quality deterioration connected to the process of applying the corset. That is why we should consider the benefits and disadvantages of a corset for such patients. Patient no. 6 was not

provided with a corset due to the reasons described above.

In the rehabilitation of patients with multiple myeloma, we should also consider exercises which are not too intensive. This helps to counteract the effects of long-lasting immobility with the symptoms of joint dysfunctions, muscle weight loss, increased risk of venous thrombosis, deterioration of cardiorespiratory sufficiency, metabolic dysfunctions and increased risk of decubitus ulcers [12]. This is especially important in patients with neurological lesions during the course of spinal cord compression syndrome. Proper physiotherapy allows the maintenance of the appropriate length of muscles, which significantly facilitates patient care.

In walking patients, attention has to be paid to safety of movement and the possibility of providing the patient with crutches, a cane or zimmerframe.

Rehabilitation of patients with multiple myeloma has to be conducted in accordance to the basic rule of improving in functioning and quality of life in palliative care, formed by Fulton and Else, which says that it should be carried out: "often but in small doses" [13]. The exercises cannot be too intensive and they cannot cause an escalation of pain. A single therapeutic session should not last too long but should be repeated 2–3 times a day. It is, therefore, extremely important to engage the family in patient care. This also allows for continuing rehabilitation at home, according to instructions provided by the therapist.

In order to optimize the quality of life of the patients, proper orthopaedic treatment in accordance with bone lesions is essential. As prophylaxis, we should also consider stabilization of the long bones with the use of intramedullar wire fixation to prevent fractures and secondary pain syndromes. Vertebral fractures are usually accompanied by severe pain and often require surgery. This pain is often only partly responsive to opioids. If it is connected with a lesion of the nervous structures and neuropathic pain is diagnosed, then it is necessary to administer coanalgetics [1–3, 6, 14]. In the case of patient no. 3, percutaneous vertebroplasty diminished the pain almost totally. The patient required only small doses of weak opioids (tramadol) and a Jewett corset. In the case of patient no. 1 (with a vertebral fracture of L2), the surgeons withdrew from the planned operation due to the decrease of pain and advised a Jewett corset. Patient no. 6 had a pathological fracture of the right radial bone, which was orthopaedically protected (Figures 1 and 2).

Pathological lesions of the spine may lead to spinal cord compression. Therefore, sudden neurological syndromes in the lower limbs and pain escalation require immediate diagnosis. Apart from spinal cord compression, nerve roots may also be compressed. It is important to establish diagnosis before irreversible neurological lesions appear (left side paralysis) and to implement an appropriate course of treatment (local radiotherapy or operation). In the case of any suspicion of spinal cord or nerve root compression, large doses of steroids should be administered until diagnosis and the establishment of a therapy plan [1, 2, 6, 14].

Delayed diagnosis and significant local development of lesions around the spine and chest in the case of patient no. 6 made neurological treatment impossible. Patient no. 4, apart from spinal pains, had left leg aesthesia disorders with coexistent muscular atrophy and debility of muscle strength.

In patients with neoplastic metastasis to the bones, bisphosphonates are especially important. Their administration prevents the appearance of skeletal-related events, helps to ease bone pain and improve the quality of life. Results of randomized trials confirmed the efficacy of these drugs in bone complications in patients with myeloma [2, 3, 15, 16]. American Society of Clinical Oncology (ASCO) established guidelines connected to the appropriate choice of bisphosphonate and indications for its administration [17]. In the case of multiple myeloma with osteolytic lesions in radiological test, it suggests administering pamidronate by intravenous infusion in a dose of 90 mg or zoledronate 4 mg every 3–4 weeks (with dose adjustment according to renal function) until the clinical efficacy of the drug is exhausted [17]. The risk of renal toxicity is reduced by adhering to the recommended dose and infusion rate, ensuring adequate hydration, monitoring renal function and adjusting the dose as appropriate or discontinuing treatment if there is deterioration, and avoiding the concurrent use of other nephrotoxic drugs. Both drugs are advised for the therapy of pain caused by osteolytic lesions and following radiotherapy, after operational procedures of spinal stabilization in patients who take typical analgesics in pain therapy [17]. Among the analyzed patients, bisphosphonates were administered to all (intravenous infusions were provided to 2 patients during the therapy).

Another difficulty in the treatment of patients with multiple myeloma is connected to chronic renal disease resulting from nephropathy that is secondary to myeloma or coexistent renal disease of

another type. At the moment of diagnosis, 30% of patients already suffer from chronic renal disease, in 50% it will develop and 20% suffer from significant renal failure, which is irreversible despite hydration and diuresis. Simultaneous diagnosis of developed chronic renal disease and multiple myeloma concerns 12% of patients. Nephrologists qualify patients for haemodialysis in the 5th stage of chronic renal disease. It is assumed that the performance of chronic haemodialysis in patients with myeloma with coexistent developed chronic renal disease provides the possibility of prolonging a patient's life by 17–20 months. It is assumed that 20% of patients die during the first month, with one-third living a further 3–5 years. However, half of the patients with diagnosed chronic renal disease are expected to improve their condition between the 30th and 70th day of the appropriate treatment. That is why hydration is especially important in these patients, especially in those with diagnosed chronic renal disease prior to chemotherapy.

Intravenous infusions of 0.9% NaCl are suggested before treatment with cystostatics in order to achieve diuresis of 2–3 litres a day. It is important to prevent urine acidaemia and, because of this, oxydasis inhibitors are administered (the best is allopurinol) before chemotherapy. If the patient has been diagnosed as suffering from chronic renal disease, it is difficult to select an appropriate cystostatic treatment, especially when establishing an effective but non-toxic dose of melphalan. Instead of MP, it is more beneficial to administer only corticosteroids or multi-drug schemes which do not include melphalan. In patients with a high concentration of M-protein in the blood serum, we may perform plasmapheresis (as in patient 2) [2, 3, 6, 18, 19].

Multiple myeloma also frequently involves hypercalcaemia. Its early symptoms (drowsiness, loss of muscle strength, depression, moderate abdominal pain, constipation and loss of appetite) can remain unnoticed. Nausea (even severe), dementia and mood changes may also appear. The basis of hypercalcaemia treatment is intravenous administration of bisphosphonate. Improvement of diuresis with furosemide and the administration of steroids may also be helpful. In reoccurrence of hypercalcaemia, it may be necessary to administer calcitonin, especially in patients with chronic renal disease, where it is necessary to avoid bisphosphonates due to increased levels of creatinine and phosphates [6, 14, 18–21]. In two of the described patients, only a temporary increase of plasma calcium concentration was observed (patients no. 1 and no. 4).

Multiple myeloma as one of fast proliferating neoplasms is associated with the risk of acute tumor lysis syndrome (ATLS). Rapid disintegration of cells during chemotherapy causes a sudden secretion of large quantities of potassium, phosphates and nucleic acids metabolized into uric acid. Secondly, renal dysfunctions appear, especially if the process is accompanied by dehydration [20].

All the observed patients had secondary anaemia (during the course of the basic disease, after chemotherapy, or secondarily to chronic renal disease). This required a transfusion of red blood cells in some of the patients during each planned hospitalization. In patients with myeloma, the administration of androgens or erythropoietin may be beneficial in order to induce erythropoiesis. The increase of haemoglobin concentration during the subcutaneous administration of erythropoietin can be observed after a few weeks and discontinuation of this therapy causes a relapse of anaemia [2, 3, 6]. In the observed patients erythropoietin was not administered.

Some of the patients may exhibit symptoms of hyperviscosity syndrome connected to a high concentration of M-protein. In the case of patient no. 1, frequent bleeding from the nose and mucous membranes of the mouth as well as from the anus was observed. They twice became a reason for emergency hospitalization. There were haematocoles on the patient's skin. The patient was administered with antihaemorrhagic drugs, strengthening and tightening the endothelium of the blood vessels. In the treatment of hyperviscosity syndrome we may use cystostatics, large dosages of corticosteroids and perform plasmapheresis.

In the case of patient no. 5, elevated body temperature was observed, along with temporary fever with no visible source of infection. The patient also reported increased perspiration, which could be partly explained by the subfebrile conditions. The patient was treated with paracetamol and NSAIDs.

Patients with multiple myeloma are a great challenge in palliative care due to the highly changeable clinical course of the disease, repetitive relapses and remissions. Numerous and often secondary coexistent symptoms require constant control and the appropriate treatment, and demonstrate that simultaneous multi-specialist care based on the collaboration of doctors from different specialties and cooperation between the patient's home and the hospital are essential. Patients with multiple myeloma require constant therapy according to the specificity of the particular stage of the disease. Apart from the chemotherapy, special attention

should be paid to the renal function, anaemia requiring blood transfusion, and frequent infections, which often require antibiotic therapy. Administration of bisphosphonates may reduce the incidents of hypercalcaemia and simultaneously support treatment of bone pain.

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