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CASE REPORT

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Effectiveness and safety of ixazomib–lenalidomide––dexamethasone in high-cytogenetic-risk relapsed/ /refractory multiple myeloma — results of the Polish Myeloma Group observational study

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Abstract

The survival of patients with multiple myeloma (MM) has significantly improved in recent years due to the introduction of new drugs such as proteasome inhibitors (PI) or immunomodulatory drugs (ImiDs). However, MM is still an incurable condition, with very variable clinical course.

The group of patients with especially poor prognosis are individuals with relapsed/refractory multiple myeloma (RRMM) with specific cytogenetic disorders — del(17p), t(4;14), t(14;16). Among the therapies that are currently in use the ixazomib–lenalidomid–dexamethasone (IRd) is considered as a candidate to improve outcome.

In this study, we analyzed the cases of patients diagnosed with high-risk molecular RRMM, who have been treated with the IRd chemotherapy regimen. An aggressive case report with no known cytogenetic data was also added. The data was collected from four centers in Poland as part of the Polish Myeloma Group observational study.

The results suggest high efficacy and good safety profile of IRd therapy in patients with RRMM and unfavorable cytogenetics.

Key words: ixazomib, lenalidomide, high risk, cytogenetic, relapsed/refractory multiple myeloma

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Introduction

Multiple myeloma (MM)/plasma cell myeloma (PCM) is a chronic, incurable neoplastic disease characterized by a clonal expansion of neoplastic plasma cells having the ability to produce pathological monoclonal protein. Its clinical course is very diverse and estimated survival is from 2 to over 10 years. Disease relapse is a common problem even after achieving complete remission. Any treatment given, by destroying drug-sensitive clones, favours the selection of more aggressive clones with cumulative genetic aberrations. In cases of chemoresistance, the chances to achieve clinical response are relatively slim [1].

The most important factors having influence on the prognosis of MM patients include defined cytogenetic abnormalities. "High risk" aberrations detected routinely by fluorescence *in situ* hybridization (FISH) include translocations t(4;14), t(14;16), t(14;20), deletion of chromosome 17p [del(17p)], hypodiploidy and 1q21 amplification [2–5].

Undoubtedly among the entire population of patients with MM — as a particularly unfavourable group prognostically — is a group with a resistant/refractory form (RRMM, relapsed/refractory multiple myeloma) with unfavourable cytogenetic aberrations. The selection of appropriate therapy becomes the key for such patients. Treatment strategies that have become promising include a combination of a proteasome inhibitor (PI) with lenalidomide/pomalidomide, double autologous stem cell transplant or a combination of immunotherapy with the use of lenalidomide/pomalidomide [6]. Nevertheless, there is a need for additional active treatment options, including regimens that will allow long-term treatment and disease control. Among those new currently used options, hopes are put on triple-drug therapy regimen ixazomib––lenalidomide–dexamethasone (IRd).

Ixazomib is the first oral PI which in combination with lenalidomide–dexamethasone (Rd) has been approved for the treatment of patients with MM after at least one previous line of treatment [7]. In the TOURMALINE-MM1 registration trial, ixazomib showed significant improvement in disease progression-free survival (PFS) (median PFS 20.6 vs. 14.7 months) and a higher response rate, with limited additional toxicity. What is particularly interesting, thanks to this treatment, the results were equalled in patients with high and standard cytogenetic risk [8].

Ixazomib is currently available for patients in Poland within an early access program. The paper presents the first Polish clinical observations of patients diagnosed with RRMM who were treated with IRd chemotherapy.

Case report studies

Case 1

A 73-year-old male with second relapsed multiple myeloma/lambda light chain disease and multiple cytogenetic aberrations (del17p, amp1q21)

In December 2016, a 68-year-old man was admitted to the medical ward of a district hospital due to increasing weakness and symptoms of worsening heart failure. Based on medical history he was diagnosed with gastric ulcer, diverticular disease and sigmoid polyp, permanent atrial fibrillation, hypertension. Within the last 3 months, the patient had been hospitalized due to embolus of the left popliteal artery and pneumonia of the left lung as well as *Staphylococcus aureus* sepsis. He was treated with an embolectomy and received intensive antibiotic therapy. The patient was on long term pantoprazole, telmisartan, enoxaparin, acetylsalicylic acid, clopidogrel, spironolactone and furosemide. He received iron supplementation parenterally due to iron deficiency anaemia in 2020.

Laboratory tests on admission showed moderate macrocytic anaemia (haemoglobin concentration [Hb] 9.3 g/dL, mean corpuscular volume [MCV] 95.0 fL), reduced iron concentration (Fe 40.23 μg/dL), elevated ferritin (431.1 ng/mL) and high concentration of C-reactive protein ([CRP] 98.9 mg/L). Based on the results of imaging tests performed, i.e., gastrointestinal endoscopy and computed tomography (CT) of thorax and abdomen no obvious cause of anaemia was found. Diagnostic bone marrow trephine biopsy was carried out.

The obtained trephine biopsy was reported as medium hypercellular (20–40% of marrow spaces), normal haematopoietic lineages were significantly reduced, abundant interstitial infiltrate with plasma cells (CD138+, immunoglobulin free light chains lambda+, kappa–) were comprising about 80% of all cells.

The patient was referred to the Department of Hematooncology and Bone Marrow Transplantation of the University Hospital in Lublin in order to complete diagnostics and treatment. Serum protein electrophoresis did not confirm monoclonal protein band but significantly increased concentration of lambda free light chains (FLC) in serum 5095.37 mg/L was found with a concentration ratio of lambda/kappa chain of 622 mg/L. A CT scan of the skeleton revealed generalized osteoporosis of bone structures and the presence of multiple disseminated osteolytic lesions (the largest with

dimensions 18 × 13 mm) in the bones of the skull, cervical and thoracic spine, femurs, tibiae and fibulae. The diagnosis of MM/lambda light chain disease was established, stage II according to the Durie-Salmon scale, II according to the International Staging System (ISS).

The patient was qualified for first-line chemotherapy bortezomib–cyclophosphamide–dexamethasone (VCD). Treatment started in February 2017 with standard doses: 1.3 mg/m^2 bortezomib on days 1, 4, 8, and 11; 500 mg/m^2 cyclophosphamide on days 1 and 8, 40 mg dexamethasone on days 1–4 and 8–11 of 28-day cycles. At the same time, supportive treatment with zolendronic acid was started as well as antibacterial and antiviral prophylaxis (sulfamethoxazole + trimethoprim, acyclovir). During treatment episodes of hyperglycaemia up to 300 mg/dL were observed, which necessitated the implementation of insulin therapy and reduction of dexamethasone dose to 12 mg on days 1–2, 4–5, 8–9 and 11–12. After 6 treatment cycles, very-good partial remission of the disease (VGPR) was reported, with a decrease in the concentration of lambda FLC in serum to 455.52 mg/ /L (approx. 91%). In August 2017, a diagnostic coronary angiography was performed, followed by right coronary artery angioplasty (PTCA RCA, percutaneous transluminal coronary right coronary artery angioplasty) with metal stent implantation (BMS, bare-metal stent). Because of comorbidities autologous haematopoietic stem cell transplantation (auto-HSCT) procedure was not performed. Given the infective complications (pharyngitis, pneumonia) and hypogammaglobulinaemia (IgG 3.3 g/L, IgM 0.25 g/L, IgA 0.5 g/L), it was decided to end the treatment in October 2017 after completion of 7 cycles of chemotherapy, starting immunoglobulin replacement therapy and close observation.

In January 2018, just after 3 months after the end of VCD chemotherapy, the patient developed disease progression (PD), increased concentration of lambda FLC up to 1036.61 mg/L. Second-line treatment was initiated according to thalidomide–dexamethasone (TD) protocol. Thalidomide 100 mg/day and dexamethasone 12 mg on days 1–4 of the 28-day treatment cycle were given. During chemotherapy, polyneuropathy to degree 3 according to NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) was observed. The treatment was stopped in December 2018, after completed 10 cycles, obtaining disease stabilization (SD, stable disease). Lambda FLC concentration lowered to 674.0 mg/L (approx. 35%).

In February 2018 an increase in lambda FLC concentration to 1204.6 mg/L was noted. The patient reported deterioration of his general condition, weakness. In laboratory tests, again anaemia (Hb 10.5 g/ /dL) was observed. Given the aggressive course, short periods of disease remission, a decision was made to extend the diagnostics with a cytogenetic examination of the bone marrow. The patient was qualified for the next line of chemotherapy according to the lenalidomide–dexamethasone (Rd) regimen. Lenalidomide 25 mg/day and dexamethasone 20 mg were recommended on days 1–4, 8–11 and 15–18 of 28-day cycles. FISH revealed complex molecular aberrations, *TP53* deletion in 36% and *CKS1B* gene amplification (*locus* 1q21) in 100% of plasma cells examined. Due to this, a request for treatment with ixazomib within the early access program was made. Ixazomib was added to therapy from Rd treatment cycle 2 at the dose of 4 mg on days 1, 8 and 15. Subcutaneous administration of immunoglobulins was continued. During treatment, upper respiratory tract infection and grade 3 pneumonia were reported. The severity of peripheral polyneuropathy reduced to grade 1 in the lower limbs. From treatment cycle 6, the lenalidomide dose was reduced to 15 mg/day. With the treatment administered, disease control at the SD level was achieved. The deepest response was noted after the 4th treatment cycle with lambda FLC concentration decrease to 614.52 mg/L (by around 49%). The patient received a total of 12 treatment cycles. In May 2020, there was a progression with an increase in lambda FLC up to 1090.0 mg/L. The patient is undergoing another line of chemotherapy according to the pomalidomide–dexamethasone (Pd) protocol.

Case 2

A 73-year-old male with relapsed IgG kappa multiple myeloma (del17p)

In June 2017, a 72-year-old man with monoclonal gammopathy was admitted to the Department of Haemato-Oncology and Bone Marrow Transplantation in Lublin for further diagnostics. The patient reported weakness being present for the last few months, periodically night sweats and bone pain. About 5 months earlier, the patient had been hospitalized for right lung pneumonia on a medical ward of a district hospital. In laboratory tests he had been found then to have mild normocytic anaemia (Hb ~11.5 g/dL), ESR around 100 mm/h and presence of monoclonal IgG kappa protein in serum (M protein 3.06 g/dL in January 2017). The patient was treated for hypertension and chronic obstructive pulmonary disease (COPD).

In control laboratory tests anaemia was confirmed (Hb 11.3 g/dL), while calcium levels were noted to be normal (Ca 2.17 mmol/L) as well as creatinine (0.9 mg/dL). A distinct protein M peak was present on serum protein electrophoresis IgG kappa 3.79 g/dL, kappa FLC concentration was 52.06 mg/L, and kappa/lambda chain ratio — 24.56. Bone marrow aspirate revealed an increased percentage of plasma cells expressing kappa light chains on immunophenotypic assessment — about 20%. CT skeletal survey showed features of osteoporosis with disseminated osteolytic foci (the largest with a dimension of 20 mm) within the vertebrae, right femur, left humerus and foot bones. Results of FISH examination showed *TP53* gene deletion — 8%. Eventually, the diagnosis of MM IgG kappa stage III according to the Durie-Salmon scale and stage II ISS was made.

The patient was qualified for the first-line chemotherapy according to the bortezomib–thalidomide–dexamethasone (VTD) protocol. The treatment commenced in July 2017. Bortezomib was given 1.3 mg/m^2 on days 1, 4, 8, and 11; thalidomide 100 mg/day, dexamethasone 20 mg on days 1–4 and 8–11 of 28-day treatment cycles. Thromboprophylaxis was recommended [subcutaneous (s.c.) enoxaparin], antiviral (acyclovir), antibacterial (sulfamethoxazole + trimethoprim) and supportive treatment with disodium pamidronate. During treatment, grade 3 neutropenia, constipation, peripheral oedema and peripheral polyneuropathy were periodically observed. Symptomatic drugs were given, and it was decided to reduce the dose of dexamethasone to 10 mg on days 1–4 and 8–11 from cycle 4. The treatment was stopped after 5 cycles due to polyneuropathy NCI CTCAE grade 3, achieving partial remission (PR) with reduction of M protein concentration to 0.49 g/dL (approx. 87%). The patient did not qualify for auto-HSCT due to advanced age and co-morbidities.

In October 2018, the patient developed PD with IgG kappa M protein increase to 1.09 g/dL. In control routine laboratory tests, no significant abnormalities were observed. The patient did not report any symptoms. Signs of polyneuropathy subsided; they were assessed as grade 1 in the lower limbs. The patient was qualified for the second-line chemotherapy according to IRd. Administered doses: 4 mg of ixazomib on days 1, 8 and 15, 25 mg of lenalidomide on days 1–21, 20 mg of dexamethasone on days 1, 8, 15 and 22. Thromboprophylaxis was continued as well as antiviral and antibacterial prophylaxis and treatment with disodium pamidronate. The treatment was tolerated very well. The patient has received so far 12 chemotherapy cycles. From cycle 8 of IRd, a very good clinical response (VGPR) has been sustained, in serum protein electrophoresis oligoclonal profile, FLC normal. So far, no complications of the treatment have been observed.

Case 3

A 72-year-old woman with relapsed multiple myeloma/lambda light chain disease (del17p) with severe renal failure

In June 2017, a 70-year-old female patient with multiple co-morbidities was admitted to the Department of Hematooncology and Bone Marrow Transplantation of the University Hospital in Lublin in average general condition [Eastern Cooperative Oncology Group (ECOG) performance status 3] for further diagnostics, with profound anaemia (Hb ~7.0 g/dL) requiring transfusion of red blood cell concentrate (RBCC), severe chronic renal impairment (estimated glomerular filtration rate [eGFR] ~15 mL/min), proteinuria.

Six months earlier, the patient developed myocardial infarction after angioplasty of the left anterior descending coronary artery (PCI LAD, percutaneous coronary intervention (left anterior descending)) with drug-eluting stent (DES) implantation with an anti-proliferative effect complicated by arrhythmias with ventricular fibrillation and sudden cardiac arrest. Within the last 3 months significant weakness and weight loss approximately 15 kg. In the control laboratory tests, a gradual deterioration of kidney functional parameters was observed (creatinine ~5 mg/dL, eGFR ~10–15 mL/min), proteinuria and anaemia, ESR up to 120 mm/h.

Serum protein electrophoresis did not confirm monoclonal protein, but a significantly increased concentration of lambda FLC — 5529.43 mg/L was noted with a lambda/kappa ratio of around 265. Bone marrow aspirate showed an increased percentage of plasma cells expressing lambda light chains by immunophenotyping — about 38%. FISH examination revealed *TP53* gene deletion — 100%. CT skeletal survey showed features of osteoporosis with single osteolytic lesions. The patient was diagnosed with MM/lambda light chain disease stage III of Durie-Salmon scale, III according to ISS.

The patient qualified for first-line chemotherapy according to VCD protocol. Treatment started in July 2017, bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11; cyclophosphamide 375 g/m^2 on days 1 and 8, dexamethasone 20 mg on days 1–4, 8–11 of a 28-day

cycle. At the same time, antibacterial and antiviral prophylaxis (sulfamethoxazole + trimethoprim, acyclovir) and anticoagulant therapy (clopidogrel) were continued.

On day 4 of the first VCD cycle, the patient suddenly deteriorated. The patient reported chest pain on the left side of her chest radiating to the shoulders and scapula and vomiting. In the performed electrocardiography (ECG), ST depression in V5–V6 was seen, and in laboratory tests — cardiac troponin levels were rising. The patient with the suspected acute coronary syndrome was transferred to a cardiology department. Ultimately myocardial infarction without ST elevation (NSTEMI, non-ST-elevated myocardial infarction) was diagnosed and effective angioplasty to the left main coronary (LM) trunk was performed with implantation of antiproliferative DES.

After stabilization of the patient's clinical status, haematological consultations took place again on day 14 after the procedure. It was decided to continue VCD chemotherapy with a reduced dose of dexamethasone 8 mg administered orally (p.o.) on days 1–4 and 8–11. After completing the 1st cycle of treatment PR was achieved, a decrease in FLC concentration lambda to 2581.22 mg/L (~53.3%) was seen. During treatment periodically anaemia was observed, requiring RBCC transfusion (once/2 months) and grade 2 polyneuropathy according to the NCI CTCAE criteria. The renal function parameters stabilized (eGFR ~15–20 mL/min) with preserved diuresis, without electrolyte imbalances. The patient did not require dialysis. She received 8 VCD cycles in total. The treatment was completed in June 2018, VGPR was obtained with a reduction in lambda FLC concentration to 73.6 mg/L (~98.6%).

Disease relapse occurred shortly, 4 months after the end of treatment there was a 3-fold increase in the concentration of lambda FLC — 238.8 mg/L. Moderate anaemia was observed in control laboratory tests (Hb 8–9 g/dL) and features of chronic severe renal impairment (eGFR ~15–20 mL/min). The patient did not complain of any significant symptoms. Performance status was 2 according to the ECOG scale. Second-line chemotherapy IRd was started in October 2018 with reduced doses due to comorbidities. Doses administered: ixazomib 3 mg on days 1, 8, and 15; lenalidomide 5 mg on days 1–21; dexamethasone 8 mg on days 1, 8, 15 and 22. Antibacterial and antiviral prophylaxis was given and thromboprophylaxis (acetylsalicylic acid) was continued. During treatment recurrent urinary tract infections were observed, pneumonia requiring hospitalization and anaemia requiring RBCC transfusion on average once every 2 months. Deterioration of kidney function or cardiovascular status are not observed. Diuresis was preserved, no electrolyte imbalances were observed, eGFR was about 20 mL/min, in control echocardiography, left ventricular ejection fraction (LVEF) was around 58%. From cycle 6, VGPR is maintained with FLC reduction not less than 90%. So far, the patient has received 18 cycles of IRd chemotherapy. The treatment continues.

Case 4

A 55-year-old man with refractory plasma cell myeloma followed by another autologous haematopoietic stem cell transplantation (del17p)

A 49-year-old man was admitted to the Hematology Department of Bialystok University Hospital in October 2011, without a previous history of chronic illnesses, for diagnostics towards MM. On admission, the patient reported bone pain, especially in the lumbosacral spine, drenching sweats and general weakness. Objectively L/S spine movement limitation was present. On FBC and blood film no significant abnormalities were found apart from erythrocyte rouleaux. In biochemical tests, a high concentration of total protein [(TP) = 12.9 g/dL] was detected with the peak of paraprotein in the gamma globulin fraction. On serum immunofixation two monoclonal protein fractions (bands) were found: 1) IgG kappa 5.78 g/dL and 2) IgG kappa 0.32 g/dL. Calcium and serum creatinine concentration remained normal and $beta_2$-microglobulin was 10.2 mg/L. Bone marrow aspirate and trephine biopsy were performed; marrow aspirate was hypercellular with 32% plasma cell infiltration, while histopathological assessment of the trephine revealed 60% plasma cell infiltration. X-ray skeletal survey revealed generalized bone porosis, numerous osteolytic lesions in the bones of the skull vault, clavicles, scapulae, ribs, sternum, long bones, pelvis and vertebrae. Moreover, CT of the spine revealed a tumour formation, dimensions approximately 47 × 41 × × 14 mm destructing Th10 vertebral body, partially indenting into to the lumen of the spinal canal with secondary stenosis and compression fracture of the Th2 vertebral body with the presence of soft tissue mass with dimensions of 21 × 20 × 11 mm with slight spinal canal stenosis as well as a pathological mass within the L2 vertebral body on the right with dimensions of 40 × 18 × 14 mm involving the arch with the vertebral body height compression. IgG kappa MM C(–) R(–) A(–) B(+) ISS stage III was diagnosed.

As initial treatment, two plasmapheresis (plasma exchange) procedures were performed and then systemic chemotherapy along with standard supportive and prophylactic treatment were started. From October 2011 to April 2012 one CD (cyclophosphamide, dexamethasone) course and four CTD (cyclophosphamide, thalidomide, dexamethasone) courses were administered. Thereafter, treatment was stopped due to critical ischaemia of the left lower limb during arterial embolism resulting in supracondylar limb amputation in April 2012. In August 2012, the disease status was assessed, and the patient remained in partial response. Chemotherapy according to CTD was continued; two further consecutive courses were given achieving a very good partial response. Additionally, the patient underwent two vertebroplasties of the lumbar vertebrae. As part of treatment consolidation, high-dose chemotherapy was administered followed by autologous haematopoietic stem cell transplantation (auto-SCT, autologous stem cell transplantation) in a tandem sequence [April 2013 after conditioning with total bone marrow irradiation (TMI, total body irradiation) and August 2013 after conditioning with high doses of melphalan (HD-Mel, high-dose melphalan)]. After administered treatment, the patient maintained VGPR. For the next 4.5 years, the patient was under outpatient clinic follow-up.

The first disease relapse occurred in October 2017: there was an increase in monoclonal protein level to 3.7 g/dL, there was bone marrow infiltration on trephine biopsy up to 50% and new bone lytic lesions were found. VCD chemotherapy was administered according to standard protocol with supportive treatment. The therapy was complicated by worsening polyneuropathy and respiratory tract infections, which led to treatment interruptions. In February 2018, on the reassessment of the disease status after four VCD courses — the stable disease was noted with the presence of M protein concentration 2.7 g/dL and with persistent plasma cell infiltration of approximately 25% on histopathological examination. In cytogenetic studies, deletion 17p was found. IRd therapy was initiated according to the standard protocol: ixazomib 4 mg on days 1, 8, and 15 + lenalidomide 25 mg for 21 days and dexamethasone 40 mg on days 1, 8, 15 and 22.

In April 2019, the patient had completed 14 IRd courses. Disease status reassessment revealed partial response to treatment with reduction of plasma cell infiltration to less than 10% on trephine biopsy. The patient qualified for another autologous transplantation. In October 2019, the patient underwent mobilization with intermediate doses of cytosine arabinoside (ID-Ara-C, intermediate Ara-C), as a result of which haematopoietic stem cells were harvested. In December 2019, third high-dose chemotherapy followed by auto-SCT was carried out. As a treatment result, the patient has achieved a continued partial response (10 months from auto-SCT). During that treatment, no more severe than grade II according to CTCAE complications were noted, treatment tolerance was fully satisfactory.

Case 5

A 55-year-old female with relapsed plasma cell myeloma after autologous hematopoietic stem cell transplantation, with planned subsequent allogeneic hematopoietic stem cell transplantation [t(4;14) and chromosome 11 trisomy]

In January 2015, a 55-year-old female patient was diagnosed with MM based on the histopathological assessment of material taken during the treatment of pathological neck fracture of the femur. Mobilization was carried out after four cycles of VTD treatment and haematopoietic stem cells collected in Lodz centre. After another two VTD cycles, the patient underwent treatment with a transplant. Disease status before the first transplantation [MEL-200 (melphalan 200 mg/m^2) — 30/11/2015] a very good partial response, complete response before the second transplantation [MEL--140 (melphalan 140 mg/m^2) — 11/04/2016]. Then maintenance treatment with thalidomide was continued for 6 months (finished in December 2016).

In January 2019, the patient developed severe bone pain. Immunohistochemical assessment of trephine biopsy confirmed disease progression. From February 2019, treatment with IRd was administered with very good tolerance, improvement of general condition and improvement of bone pain. The patient has received 20 cycles of IRd treatment so far which has been tolerated. Bone pain subsided. A complete response has been achieved. Due to past tandem transplantation, high cytogenetic risk [t(4;14) and chromosome 11 trisomy] and short first remission, the patient was qualified for allogeneic bone marrow transplantation (allo--SCT, allogeneic stem cell transplantation) in the Institute of Oncology in Gliwice. On 2nd September 2020, the patient received myeloablative chemotherapy according to MEL-140 protocol.

Case 6

A 55-year-old male with second plasma cell myeloma relapse, after two autologous haematopoietic stem cell transplantations, with an aggressive course of the disease

A 48-year-old man reported to the Oncology Centre — Institute (CO-I, *Centrum Onkologii — Instytut*) in Warsaw in 2010 with a several-month history of severe bone pain and suspicion of osteolytic lesions in the spine vertebrae based on X-ray examination of the thoracolumbar spine carried out in primary care. Diagnostics carried out in CO-I revealed: disseminated osteolytic lesions, most severe in the thoracic and lumbar spine, sacrum, pelvis and sternum, high protein M concentration in serum (32 g/L) in IgG class with kappa light chains, anaemia with Hb concentration of 10.2 g/dL and 35% bone marrow infiltration by plasma cells. MM in stage IIIA according to the Durie-Salmon scale and IIIA according to the ISS was diagnosed.

The patient qualified for induction treatment according to the CTD regimen with the transplant procedure as a plan. The patient received 8 CTD courses, yielding VGPR. During the induction treatment, successful mobilization and collection of stem cells with high doses of cyclophosphamide and granulocyte colony-stimulating factor (G-CSF) were carried out. Simultaneously with induction treatment supportive treatment with bisphosphonates was given, and after stem cell harvesting the patient underwent irradiation to the most destructive lesions of the skeleton, i.e., to Th10–S5 area. In 2011, after myeloablative therapy MEL-200, auto-SCT was performed, 2.7×10^6 CD34/kg body weight were administered. Due to persistent VGPR after auto-SCT, the patient qualified for thalidomide maintenance treatment, which was given until disease progression, i.e., for 3 years (2011–2014). In 2014, in the absence of clinical symptoms, based on routine control blood and urine tests, PD was diagnosed. The serum concentration of TP was increased as well as the concentration of FLC was significantly increased in serum with an abnormal FLC ratio and presence of Bence-Jones protein in the urine (initially absent). Further diagnostics showed again 30% marrow involvement by plasma cells and the presence of new osteolytic lesions in the skull, ribs and bones of the limbs. At that time, no adverse cytogenetic prognostic factors were found. The patient was qualified for a second-line systemic treatment according to the PAD regimen (bortezomib, doxorubicin, dexamethasone) which turned out to be ineffective — after four courses no satisfactory response was achieved (less than PR). Additionally, the patient developed side effects: grade 3 neutropenia and grade 3 peripheral polyneuropathy (therefore, the patient required G-CSF and bortezomib dose reduction). As a third-line treatment, individual chemotherapy CE (cyclophosphamide, etoposide) was given. After six CE courses, PR was obtained, again mobilization and collection of stem cells with high doses of cyclophosphamide and G-CSF (plerixafor) were performed. In 2015, a second transplant procedure was performed, 4.1×10^6 CD34/kg body weight were administered. Again, on disease response assessment to auto-SCT, VGPR was noted which lasted for 2 years. In 2017, a second disease progression occurred; a massive concentration of M protein was present in serum (IgG 6000 mg/dL), high kappa FLC concentration in both serum and urine, anaemia and thrombocytopenia. In September 2017, the patient started fourth line systemic treatment with lenalidomide, ixazomib, and dexamethasone. After 12 months of therapy, a very good effect of treatment was achieved: normalization of TP concentration, a significant decrease in IgG concentration and normalization of serum FLC ratio. Blood counts improved significantly — no thrombocytopenia or anaemia. In the latest protein control studies in September 2018, M protein IgG kappa in serum was sustained and Bence-Jones protein in low concentrations (response was assessed as VGPR). The patient continues treatment with good haematological tolerance, but dexamethasone dose reduction was required due to undesirable signs of steroid therapy. A very good laboratory response to treatment is shown in Figures 1 and 2.

Discussion

Treatment of patients with RRMM in everyday clinical practice is challenging. Despite enormous progress linked to the implementation of PI and ImiD, MM remains an incurable disease. Nowadays the basis for the therapy of this disease entity are modern two-, three- and even four-drug protocols consisting of ImiD, PI, corticosteroids, monoclonal antibodies and classical chemotherapeutic agents [9, 10].

According to the international prognostic scoring classification, the 5-year survival rate in the R--ISS stage equal to 1 is 82%, in the R-ISS stage equal to 2 — 62%, while in the R-ISS stage equal to 3 — only 40%. Factors determining worse prognosis in R-ISS stage equal to 3 are $beta_2$-microglobulin concentration above 5.5 mg/L, increased activity of serum lactate dehydrogenase

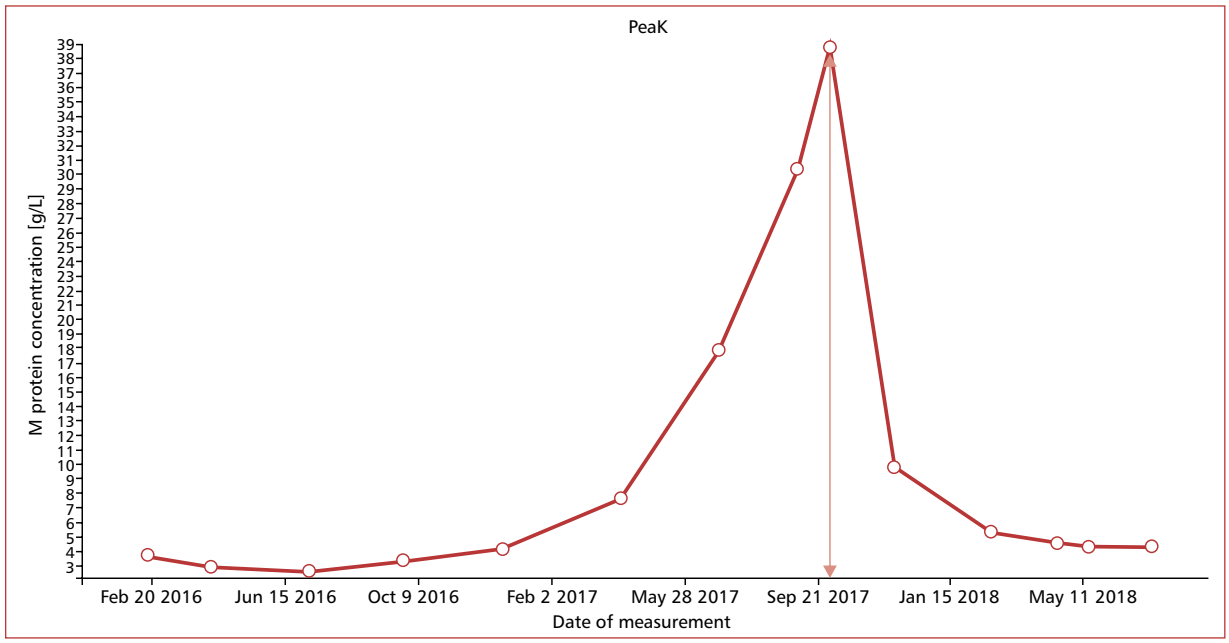

Figure 1. Reduction of M-protein peak in serum protein electrophoresis as a result of treatment with IRd (ixazomib, lenalidomide, dexamethasone). The arrow indicates the start time of IRd treatment

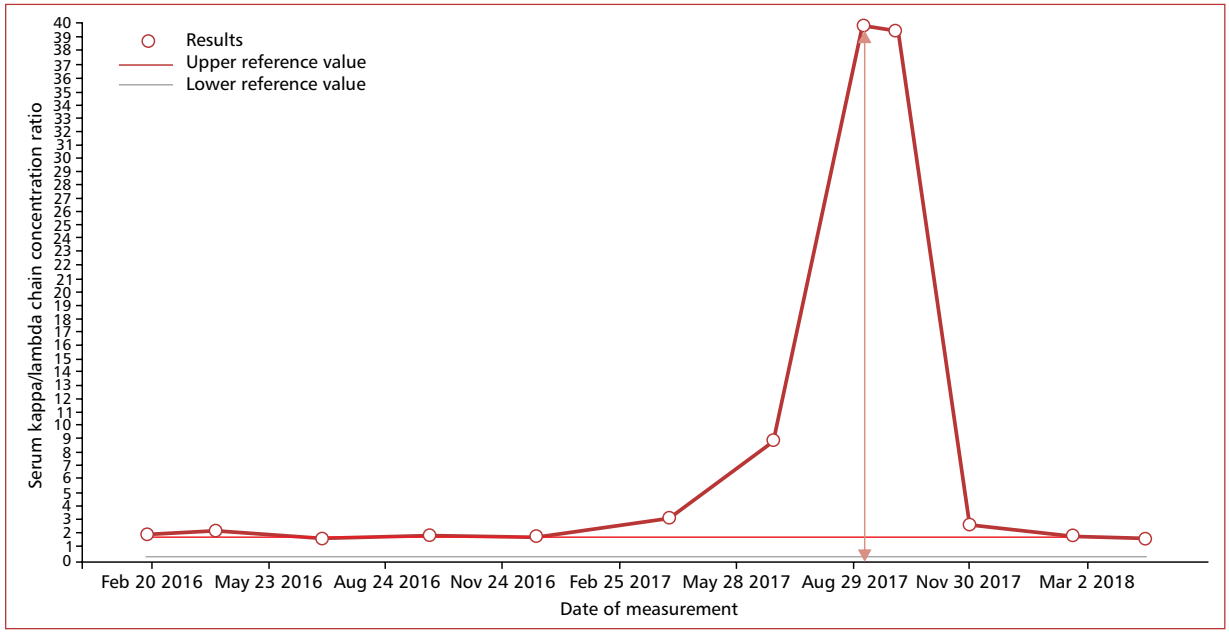

Figure 2. Dynamics of changes in the value of lambda free light chains (FLC) in serum during treatment according to IRd regimen (ixazomib, lenalidomide, dexamethasone). The arrow indicates the start time of IRd treatment

(LDH) and/or presence of adverse cytogenetic aberrations, such as del17p, t(4;14), t(14;16) [11].

High-risk cytogenetic aberrations in patients with MM are of particular therapeutic challenge. Chromosomal aberrations in neoplastic cells lead to the development of resistance, which translates into a reduction of complete and deep response rates to treatment and shortening the time to PFS and overall survival (OS) [12]. Due to unsatisfactory treatment results of high-risk MM new drugs

and regimens are being sought with higher efficacy and not increased toxicity at the same time [13].

Proteasome inhibitors are a group of drugs that bind to the proteasomal complex, leading to blockage of chymotrypsin-like activity, which in turn causes the accumulation of abnormal proteins in the cell and the activation of apoptosis cascade [14]. The first PI widely used in anti-cancer therapy is bortezomib, which rapidly and reversibly inhibits the activity of the proteasome, resulting in decreased expression of proteins responsible for survival, growth and proliferation of neoplastic cells. The drug is administered as an intravenous or subcutaneous injection. The side effect profile is predominately haematological toxicity and polyneuropathy and infections [15]. Second generation PIs are of much lower risk of neurotoxicity; irreversible PI carfilzomib and reversible PI ixazomib [16].

Used in the presented cases ixazomib within the IRd regimen is the first oral PI approved for the treatment of MM. The drug binds preferentially to the beta 5 subunit of the proteasome, resulting in induction of apoptosis activation in myeloma cells. Registration indications include treatment, in combination with lenalidomide and dexamethasone, in adult patients with MM who previously received at least one line of therapy [15]. Particularly noteworthy is the fact that in the TOURMALINE--MM1 registration study an increase in PFS from 9.7 to 21.4 months was observed in the group of patients with high-risk myeloma associated with cytogenetic aberrations del17p, t(4;14), t(14;16). Also, no additional toxicity was observed with the addition of ixazomib to Rd therapy [8]. Ixazomib has been also studied in subpopulations of patients with unfavourable cytogenetic changes and PFS prolongation was demonstrated in different patient groups: with del(17p) [hazard ratio (HR) 0.596, 95% confidence interval (CI): 0.286–1.243], amplification 1q21 (HR 0.781, 95% CI: 0.492–1.240) and the group of patients with coexistence of adverse cytogenetic changes and/or 1q21 amplification (HR 0.664, 95% CI: 0.474–0.928) [17].

Both, the current clinical recommendations of the Polish Myeloma Group and the American National Comprehensive Cancer Network (NCCN) indicate ixazomib in combination with lenalidomide and dexamethasone for the treatment of MM patients who received at least one line of treatment [18, 19]. It is worth emphasizing that in the case of combination therapy with ixazomib, lenalidomide and dexamethasone as well as regimens containing carfilzomib improvement of OS of patients with relapsed or refractory MM has been shown [20–22].

The cases presented in this paper illustrate good treatment outcomes in patients burdened with unfavourable prognostic factors, including the presence of high-risk cytogenetic aberrations. The patients responded to treatment, which in some cases enabled the use of high-dose chemotherapy followed by autologous haematopoietic stem cell transplantation. Moreover, considering multiple comorbidities and the distance from the reference centres, the use of oral therapy with ixazomib can lead to a significant improvement of patient quality of life and reduce the risk of treatment discontinuation in clinical practice for reasons unrelated to progression or treatment toxicity [23].

Clonal evolution related to the course of myeloma treatment leads to the selection of resistant clones leading to a loss of response to therapy. Administered therapies result in the removal of clones sensitive to drugs while promoting the progression of aggressive clones [24]. Therefore, the use of multi-drug therapies with the highest possible effectiveness against different clones or subclones of myeloma cells is highly beneficial. Usually, new drugs are used in combination with traditional cytotoxic medications, which allows obtaining a good response to treatment and prolongation of PFS in most patients with RRMM [25].

In summary, an oral well-tolerated regimen containing ixazomib, lenalidomide and dexamethasone represent an important therapeutic option for all patients with relapsed or refractory MM, particularly for high-risk patients with unfavourable cytogenetic findings.

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