Short Thesis for the degree of doctor of philosophy (PhD)

Stem cell mobilization techniques and examination of certain bone marrow microenvironment biomarkers in multiple myeloma

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1 Introduction

1.1 Epidemiology

Multiple myeloma (MM) or plasma cell myeloma is an indolent lymphoproliferative neoplasm characterized by malignant proliferation of clonal plasma cells. It accounts for 1% of all cancers and 10% of hematological malignancies, thus being the second most common oncohematological disease. The incidence of the disease is 5-6/100.000 persons/year, and its prevalence is constantly increasing due to improving survival rates. It occurs predominantly in older age, with an average age of 65 years at diagnosis, and its frequency increases with age.

1.2 Pathogenesis

The development and progression of MM is the result of complex interactions between genetic, epigenetic, and environmental factors. In almost all cases, the disease originates from an asymptomatic precursor condition, monoclonal gammopathy of undetermined significance (MGUS). In MGUS, a small number of abnormal plasma cell clones (less than 10%) produce monoclonal immunoglobulins, with concentrations not exceeding 30 g/L. The probability of progression to malignant hematological disease is 1% per year. MGUS is followed by smoldering myeloma, which is an asymptomatic stage. In this phase, the bone marrow plasma cell ratio is already higher, but does not reach 60%, which is sufficient for a diagnosis of MM without clinical symptoms. Active MM with organ damage can develop over several years. The rate of progression and clinical presentation are determined by the genetic instability of the abnormal plasma cells on the one hand and the supportive effect of the bone marrow microenvironment on the other.

The underlying genetic abnormalities involved in the development of the disease can be divided into two main groups. In nearly half of the cases, hyperdiploidy (trisomy of chromosomes 3, 5, 7, 9, 11, 15, 19, and 21) is observed, which is associated with a more favorable prognosis, while in the other large group, translocations of the immunoglobulin heavy chain gene (IgH) on chromosome 14 predominate. These rearrangements lead to the overexpression of oncogenes, including cyclin D proteins, members of the MAF family, MMSET, and FGFR3, and significantly influence the biology and outcome of the disease. The five most frequently detected translocations are t(11;14), t(4;14), t(6;14), t(14;16), and t(14;20). The t(11;14) translocation is the most common, occurring in 15% of patients. During progression, additional secondary genetic abnormalities, such as 1q21 amplification and 13q or 17p deletion, may accumulate, which are associated with a more aggressive clinical course and refractoriness to

therapy. However, genetic differences alone do not explain the clinical heterogeneity of multiple myeloma. There is growing evidence that the bone marrow microenvironment plays an active role in disease maintenance, the development of drug resistance, and the occurrence of relapses.

1.2.1 Role of the microenvironment

MM is closely linked to the bone marrow microenvironment, which supports the survival of abnormal plasma cells in both structural and functional terms. The complex cell network formed by stromal cells, osteoclasts, osteoblasts, immune cells, and adipocytes produces a wide spectrum of cytokines, chemokines, and growth factors. Among these, IL-6, RANKL, and MIP-1α play a prominent role in enhancing plasma cell proliferation, promoting bone resorption, and contributing to the development of therapeutic resistance. Interactions in the microenvironment also reinforce immune escape mechanisms. Activation of the PD-1/PD-L1 axis, decreased function of effector T cells and NK cells, and proliferation of regulatory T cells allow tumor cells to avoid the immune system's recognition and elimination mechanisms. These processes are closely associated with disease progression and the occurrence of relapses.

With advancing age, adipocytes become the dominant cell component of bone marrow. Bone marrow adipose tissue is a distinct fat depot that differs from white and brown adipose tissue in terms of its origin, gene expression, phenotype, and physiological functions. There is growing evidence that adipocytes play a central role in plasma cell survival, drug resistance, and disease progression in the bone marrow microenvironment. Adipocytes are known to be metabolically active endocrine organs that produce and secrete numerous inflammatory mediators and adipokines. Adipokines are bioactive molecules that regulate inflammation, angiogenesis, metabolism, and immune responses. It has been shown that dysregulation of these adipokines promotes carcinogenesis, including MM, by creating an environment conducive to genetic instability, impairing DNA repair mechanisms, and facilitating immune evasion mechanisms, as well as directly providing a protective environment for malignant cells. Given this background, the bone marrow niche, particularly adipokines, may be promising candidates for MM biomarker research.

Adiponectin is an adipokine with anti-MM activity with tumor-suppressive effects. Its levels are higher in the preclinical phase of MM than in active disease. Leptin is a proinflammatory peptide hormone that regulates appetite and energy balance. Most data to date indicate that its levels are elevated in MM. Resistin is an adipokine associated with insulin resistance and

inflammatory processes, which may be linked to the risk of developing MM. Chemerin influences the chemotaxis of immune cells, the maturation of adipocytes, and the development of inflammatory processes in the bone marrow. Data on chemerin in MM are currently limited. Adipsin is a serine protease that plays a role in adipocyte function, the regulation of metabolic processes, and the activation of the alternative complement pathway. Adipsin is thought to be involved in the pathomechanism of bone damage associated with MM, but it has not yet been studied as a disease marker. Thrombospondin 1 (TSP-1) is one of the regulatory proteins in the bone marrow microenvironment of MM, but its level and role as a biomarker have not yet been studied in MM. Paraoxonase 1 (PON-1) is a lipoprotein that contributes to the removal of free radicals, thereby reducing sensitivity to oxidative stress. Its role in MM is not yet known. Myeloperoxidase (MPO) is an oxidative enzyme expressed in myeloid cells that helps manage oxidative stress, inflammation, and modulate the immune microenvironment. The development of MM is associated with increased production of MPO from myeloid cells. In vivo, elevated MPO levels in mouse models correlate with MM progression.

1.3 Clinical features

The clinical manifestations of MM are multiple myeloma, extramedullary plasmacytoma, and plasma cell leukemia. The clinical symptoms of MM are caused by the proliferation of abnormal plasma cells in the bone marrow and the organ-damaging effects of the large amounts of M protein they produce. Plasma cells infiltrating the bone marrow displace healthy hematopoietic cells, which can lead to anemia, thrombocytopenia, and leukopenia. Leukopenia may be accompanied by recurrent infections, which are further worsened by immunoparesis associated with decreased production of functional immunoglobulins. Myeloma cells stimulate bone resorption through increased osteoclast activity, leading to osteopenia, lytic bone lesions, bone pain, and pathological fractures. M proteins, especially free light chains, can be deposited in many organs, causing loss of function; most commonly affecting the kidneys, less frequently the heart or liver. The most common complications of MM can be summarized by the acronym CRAB: hypercalcemia (C), renal failure (R), anemia (A), and bone lesions (B). Extramedullary plasmacytoma can cause various compression symptoms.

1.4 Diagnostics

We use the International Myeloma Working Group (IMWG) recommendations to diagnose multiple myeloma. Laboratory and imaging tests targeting specific criteria are required to make the diagnosis, while other tests provide information about the prognosis and stage of the disease.

If the disease is suspected, a bone marrow sample (aspiration or biopsy) is required to confirm the presence and percentage of clonal plasma cells. The immunophenotyping of plasma cells (CD138, CD38) and the confirmation of their clonality are performed using immunohistochemical or flow cytometric methods. Genetic abnormalities play a key role in assessing the prognosis of the disease, and are primarily examined using fluorescence in situ hybridization (FISH) or next-generation sequencing (NGS). Hyperdiploidy and t(11;14) indicate a standard prognosis, while t(4;14), t(14;16), t(14;20) translocations and 17p deletion, among others, indicate a poor prognosis. Monoclonal proteins produced by plasma cells are detected in serum and urine using electrophoresis and immunofixation. Serum M-protein is most commonly of the IgG and IgA types, while the IgD, IgE, and IgM types are rare, with true non-secretory cases accounting for only about 1% of cases. Automated free light chain (FLC) immunoassays can be used to determine the absolute serum concentrations of free kappa and lambda light chains, as well as the ratio of the two values. Light chain myeloma occurs in 15-20% of patients. Additional laboratory tests include complete blood count, peripheral smear, renal function parameters, calcium, lactate dehydrogenase (LDH), albumin, and beta-2-microglobulin (B2MG). Elevated LDH levels indicate high cell proliferation activity and thus a poor prognosis. Determining serum albumin and B2MG levels is important for determining the stage and prognosis of the disease. Plasma cells detected in peripheral blood smears indicate a poor prognosis and plasma cell leukemia. Imaging tests are used to detect bone involvement and extramedullary manifestations. In addition to conventional X-rays, CT, MRI, and PET/CT scans show bone lesions, bone marrow infiltration, and soft tissue plasmacytomas with greater sensitivity. The diagnostic criteria for MM are based on the presence of clonal plasma cell proliferation reaching 10% in the bone marrow or solitary plasmacytoma confirmed by histological examination and organ damage (CRAB symptoms), as well as the confirmation of one of the three new biological factors (SLiM criteria): a bone marrow plasma cell percentage above 60% (S=sixty percent), a serum free light chain ratio above 100 (Li=light chain ratio), and more than one focal bone lesion on MRI (M).

1.5 Stage and risk stratification

A more accurate prognosis requires the combined assessment of several factors. As with other cancers, MM is affected by the patient's general condition, tumor burden (stage), biology (e.g. cytogenetic abnormalities), and response to therapy. The International Staging System (ISS) published in 2005 was used for risk stratification, which classifies patients into three risk groups

based on two easily measurable laboratory parameters, albumin and B2MG, between which significant differences in survival can be observed. The latest recommendation, published in 2014, is an improved version of this, the Revised-ISS (R-ISS), which refines the risk classification by taking into account high-risk cytogenetic abnormalities and LDH levels. The course of the disease is best indicated by the molecular subtype and the presence or absence of secondary cytogenetic abnormalities. The R-ISS therefore combines elements of tumor burden and disease biology to create a unified prognostic index that aids in practical patient care and the comparison of clinical trial data. To ensure uniform availability, only three widely available cytogenetic markers are used in R-ISS: t(4; 14), t(14; 16), and 17p deletion, the presence of which indicates high risk, while the absence indicates standard risk. Given the heterogeneity of the disease, there is a growing need to identify new, more accurate biomarkers in addition to the prognostic factors and biomarkers used in everyday clinical practice. Among others, microRNAs, angiogenesis factors, extracellular matrix proteins, telomere length and telomerase activity, and bone marrow microenvironment markers are the subject of intensive research.

The estimated prognosis of MM may vary depending on the source of the data. Based on real-life data, overall survival (OS) in patients eligible for transplantation exceeds 10 years. In elderly patients (over 75 years of age), the median OS is lower, at approximately 5 years. With the introduction of the latest therapeutic options, monoclonal antibodies, and bispecific therapies, these figures are likely to underestimate current survival rates.

1.6 Therapy

According to current knowledge, multiple myeloma is an incurable disease, therefore the goal of treatment is to achieve the deepest and longest possible remissions, delay relapse, and maintain quality of life. The therapeutic strategy is determined by the patient's general condition and comorbidities, the biological heterogeneity of the disease, cytogenetics, risk classification (ISS/R-ISS), and minimal residual disease (MRD) status. The therapeutic response is assessed based on the IMWG criteria, which determine MRD by detecting plasma cells remaining in the bone marrow and measuring serum and urine M-protein levels: MRD-negative complete response, complete response (CR), very good partial response (VGPR), partial response (PR), stable disease (SD), and progressive disease (PD).

Modern treatment is based on a combination of several drug groups with different mechanisms of action and typically consists of consecutive lines of treatment. Treatment options have improved significantly in recent decades. The use of previously administered myelotoxic

chemotherapies has declined, and they are now only used in combination in aggressive cases that do not respond to new drugs/refractory cases or in primary plasma cell leukemia, as well as in stem cell mobilization. Corticosteroids are an integral part of anti-myeloma treatment and are included in almost all drug combinations.

In addition to their angiogenesis-inhibiting effect, immunomodulatory drugs (IMiDs) enhance T-cell activity and inhibit tumor cell proliferation by activating cereblon E3 ligase. The first representative of this drug class was thalidomide, which became the standard therapy for MM in the 2000s. However, due to its severe neuropathic side effects, a more effective second-generation IMiD with a more favorable side effect profile was developed: lenalidomide, which is currently the standard therapy for MM. However, lenalidomide is bone marrow toxic and excreted by the kidneys, which makes its use problematic in cases of renal or bone marrow failure. Pomalidomide is a third-generation, even more effective IMiD, which is registered for the treatment of relapsed/refractory MM.

Following IMiDs, proteasome inhibitors have been added to the everyday therapeutic repertoire. Their targets are large intracellular protein complexes that play an important role in the DNA repair processes of tumor cells, and thus in their survival and proliferation. The first representative of this class is the reversible, parenterally administered bortezomib, followed by newer generation agents such as the irreversible, parenterally administered carfilzomib and the orally administered ixazomib.

With the advancement of immunotherapy, monoclonal antibodies targeting antigens expressed on the surface of myeloma cells have also appeared in the treatment of MM. They exert their effect through three mechanisms: in addition to direct antitumor activity, they trigger antibody-dependent cellular cytotoxicity (ADCC) reactions and complement-mediated cell lysis. The first representative of this class is daratumumab, which binds to CD38 on the surface of plasma cells and exerts complement-mediated tumor cell lysis and antibody-dependent cytotoxic effects. Isatuximab is a second-generation anti-CD38 drug. The latest immunotherapies available in Hungary only in clinical trials for RRMM include elotuzumab, which targets SLAMF-7, belantamab mafadotin, which is a BCMA (B-cell maturation antigen) molecule-targeted antibody-toxin conjugate, bispecific antibodies (teclistamab, elranatamab, talquetamab), and chimeric antigen receptor T-cell (CAR-T) therapy. Two approved representatives in MM are idecabtagen vicleucel (ide-cel) and ciltacabtagen autoleucel. Other signal transduction inhibitors can also be used in MM. Venetoclax, a Bcl-2 inhibitor, is effective in the treatment of MM patients with the t(11;14) translocation affecting the Bcl-2 gene.

Selinexor is a small molecule nuclear transport protein inhibitor that can be used in refractory-relapsed MM cases.

In MM treatment, the introduction of autologous hematopoietic stem cell transplantation based on high-dose melphalan represented a breakthrough, significantly improving both progression-free survival (PFS) and overall survival (OS) and resulting in a three-year survival rate of approximately 80%. Therefore, AHSCT remains the gold standard treatment for eligible patients in good general condition. Most MM treatment algorithms treat patients who are eligible for AHSCT after high-dose chemotherapy separately from those who are not. If the patient is eligible for high-dose melphalan autologous stem cell transplantation, the treatment plan consists of induction therapy, stem cell collection, conditioning therapy, transplantation, and then maintenance therapy, the standard form of which is currently low-dose lenalidomide. Together, these constitute first-line therapy. Despite new treatment options, this regimen continues to offer the best survival outcomes. During induction, combination therapy, known as triplet therapy, is recommended, which in most cases includes an immunomodulatory agent, a proteasome inhibitor, and a corticosteroid, supplemented with monoclonal antibodies if necessary. Currently, we mostly use the VRD (bortezomib, lenalidomide, dexamethasone) combination. More recently, even better results have been achieved with quadruplet therapies that also include daratumumab, but its availability in Hungary is currently limited for financial reasons. It is only advisable to depart from the above protocol in cases of severe renal failure, in which case cyclophosphamide can be used instead of lenalidomide. Induction usually consists of 3–6 cycles, and stem cells are collected during treatment. The deeper the therapeutic response achieved, the longer the progression-free and overall survival can be expected.
The essence of AHSCT is that we use high-dose conditioning with complete myelo- and lymphoablative effects to destroy the patient's residual tumor cells and bone marrow hematopoiesis. We then reintroduce previously collected healthy mononuclear cells, including pluripotent CD34+ stem cells, thereby rebuilding blood formation and resetting the adaptive immune system, thereby modulating the immune response against the remaining tumor. The most common indication for AHSCTs is MM. Stem cells are usually collected from peripheral blood. The mobilization of stem cells from the bone marrow into the peripheral blood was previously only achieved with granulocyte colony-stimulating factor (G-CSF) following chemotherapy. We most commonly use protocols containing cyclophosphamide, etoposide, cytarabine, or combination chemotherapy appropriate for rescue therapy. In MM, the gold standard is intermediate-dose (2-4 g/m2) cyclophosphamide, but we also use other protocols,

such as high-dose etoposide, cytarabine, or combinations, e.g., PACE (cisplatin, adriamycin, cyclophosphamide, and etoposide). Recently, we have been performing mobilization according to the G-CSF protocol more and more frequently.

The COVID-19 (coronavirus disease 2019) pandemic has made the need for this method more urgent due to fewer days spent in hospital and lower rates of infectious complications, so its use has become significantly more common since 2020. The protocol is as follows: administration of 10 ug/kg filgrastim subcutaneously for 4 days, measurement of peripheral CD34+ count on day 5 using a flow cytometer. If the measured value is at least 20 CD34+ cells/uL, leukapheresis can be started. The IMWG recommendation is at least 4×10^6/kg body weight of viable stem cells. After quality assurance testing, the stem cell preparation obtained in this way is cryopreserved with 5–10% dimethyl sulfoxide and stored in liquid nitrogen until reinfusion. Plerixafor may be administered in cases of inadequate mobilization. Plerixafor facilitates the migration of stem cells from the bone marrow and lymphatic tissue into the peripheral blood by blocking the CXCR4 receptor. It can be used if a value between 5 and 20 CD34+ cells/uL is measured on day 4 after administration of G-CSF. Stem cell mobilization can therefore take the form of chemomobilization (chemotherapy + G-CSF) +/- plerixafor, or G-CSF alone +/- plerixafor. These strategies differ in several aspects, such as stem cell yield, safety, and, last but not least, cost. The extent to which the type and duration of induction therapy and the number of therapeutic lines influence mobilization propensity is currently the subject of research. Among the new generation of first-line therapies, there is data on the mobilization-reducing properties of lenalidomide and daratumumab. It is a known fact that patients who have undergone multiple prior treatments are more likely to have weaker mobilization, so plerixafor must be used more frequently and chemomobilization is preferable. On the second day after the conditioning treatment with 200 mg/m2 melphalan, the stem cells are infused, which is the "transplantation" itself. The intravenously administered stem cells "find their way home" to the appropriate microenvironment (homing) through cytokines and adhesion molecules secreted by bone marrow stromal cells, where engraftment, division, and multidirectional differentiation occur.

In elderly patients over 70 years of age who are not eligible for AHSCT, a low-dose melphalan-containing protocol, VMP (bortezomib, melphalan, prednisolone), was previously used. Nowadays, VRd is considered the standard treatment for this group as well, but more favorable results can be achieved with combinations that also include daratumumab (Dara-Rd, Dara-

VRd). If lenalidomide is contraindicated, the VCD (bortezomib, cyclophosphamide, dexamethasone) protocol is recommended.

Second-line and subsequent treatment of MM is determined by a combination of factors, such as the patient's general condition, cytogenetic risk profile, type of first-line therapy, duration of response to that therapy, treatment-related toxicity, refractoriness to certain types of drugs, and availability of drugs. The administration of daratumumab during the first relapse is definitely beneficial. Since the combined administration of two new-generation drugs is not funded in Hungary, we are forced to combine anti-CD38 treatment with a previously used drug, taking into account the time elapsed since relapse and risk stratification. In aggressive MM that does not respond to induction, combined immunochemotherapy VTd or VRd-PACE can be used as a rescue treatment and in primary plasma cell leukemia, supplemented with anti-CD38 therapy if possible. In younger patients, if remission has been achieved for at least 2 years after AHSCT, a second AHSCT should be considered.

2 Aims

One focus of our research was to examine the clinical characteristics (age, gender, M-component type, stage, FISH risk) of our MM patients who underwent stem cell mobilization between 2018 and 2022, as well as their previous treatments and the effectiveness of stem cell mobilization. Our goal was to compare chemotherapy (Cyto+G-CSF) and G-CSF-only (Solo-G-CSF) stem cell mobilization strategies in our patients. During the analysis of the subgroups, we examined the different treatment strategies, their safety and efficacy, the effect of the active substances used on mobilization tendency, and the cost implications of the different modalities.

Another aim of our research was to examine biomarkers of the bone marrow microenvironment in our MM patients. Our goal was to explore, within the framework of a cross-sectional case-control study, how the serum levels of eight adipokines (adiponectin, leptin, resistin, chemerin, adipsin, thrombospondin-1 [TSP-1], paraoxonase-1 [PON-1], and myeloperoxidase [MPO]) in the serum of our MM patients in relation to clinical, laboratory, and molecular markers of the disease. We also planned to examine the levels of adipokines measured in MM compared to a control group of healthy individuals.

3 Patients and methods

3.1 Comparison of stem cell mobilization strategies

We retrospectively collected data on MM patients who underwent stem cell mobilization procedures at our institute, the Department of Hematology, Institute of Internal Medicine, Faculty of Medicine, Debrecen between January 2018 and December 2022. We collected clinical data on the study population regarding age, gender, clinical stage, previous treatments and responses achieved, mobilization strategy, length of hospital stay, infectious complications, and the amount of stem cells collected. The outcomes studied included mobilization failure, the need for plerixafor, the number of apheresis days, the amount of CD34+ stem cells collected, the frequency of infectious complications observed during mobilization, and the number of days spent in the hospital. ISS and R-ISS stages and response criteria were determined based on IMWG criteria, where relevant data were available. FISH results indicating a poor prognosis were t(4;14), t(14;16), and del(17p). Chemotherapy treatment included the use of medium-dose cyclophosphamide (3–4 g/m^2) or combination therapy (PACE). Filgrastim stimulation with a dose of 10 μg/kg/day was initiated when the absolute neutrophil count fell below 1000/μL. For mobilization without chemotherapy, patients received 10 μg/kg/day of generic G-CSF subcutaneously for 4 days. On the fifth day, the number of peripheral stem cells was determined by flow cytometry. In both groups, patients received 24 mg/day of plerixafor subcutaneously if the white blood cell count exceeded 5000/μL and the number of peripheral CD34+ cells was in the range of 5–20/μL. The stem cell collection procedure was initiated when the peripheral CD34+ stem cell count exceeded 20/μL. All collections were performed using the MNC program of the Spectra Optia (Terumo BCT, Lakewood, CO, USA) apheresis system. The goal was to collect at least 4x10^6 stem cells per kilogram of body weight for each AHSCT.

Categorical variables were presented based on their frequency and percentage, while continuous variables were presented based on their median and range. The Kolmogorov-Smirnov test was used to assess the normality of the data. Discrete variables were compared using the chi-square test, while analysis of variance (ANOVA) was used to measure the relationships between patient characteristics and outcomes. The t-test was used to assess whether the difference between the means of two variables was statistically significant. We used binary logistic regression and multivariate logistic regression to verify which variables have an independent prognostic role in terms of different outcomes. The threshold for statistical significance was set at $p<0.05$. Statistical power was assessed using post-hoc power analysis.

Statistical tests were performed using SPSS 26.0 computer software (IBM Corp., Armonk, NY, USA).

3.2 Examination of biomarkers

In this case-control, cross-sectional study, we collected serum samples from 40 MM patients treated at the Department of Hematology, Institute of Internal Medicine, DEKK, between November and December 2024, and analyzed their data. The diagnosis of MM and response criteria were also determined based on IMWG criteria. The clinical, laboratory, and epidemiological data of the patients, including age, sex, hemoglobin, LDH, renal function (eGFR), serum albumin, M-protein, light chain ratio, ISS and R-ISS stages, cytogenetic abnormalities determined by FISH, treatment response categories, and CRAB symptoms were collected from medical records. FISH abnormalities associated with a poorer prognosis included t(4;14), t(14;16), and del(17p) abnormalities. For comparison, serum samples were collected from a healthy patient population of 38 individuals matched for age and sex.

We measured serum levels of eight biomarkers: adiponectin, leptin, resistin, chemerin, adiponectin, TSP-1, PON-1, and MPO. Serum MPO, PON-1, TSP-1, and chemerin levels were measured using a sandwich-type enzyme-linked immunosorbent assay (ELISA). Serum adiponectin, adiponectin, resistin, and leptin levels were evaluated using a bead-based multiplex immunoassay followed by flow cytometry using the LEGENDplexTM Human Metabolic Panel 1 and Novocyte 3000 RYB flow cytometer. In our study, we compared the levels of analytes with other biomarkers and clinical characteristics of disease activity (serum LDH level, B2MG level, free κ and λ light chain concentration, albumin level, hemoglobin concentration, and eGFR). Immunofixation was used to determine the monoclonal component. The normality of the data was tested using the Kolmogorov-Smirnov test. Comparisons between groups (patients vs. controls; subgroups ISS/R-ISS, CRAB, according to response to treatment) were performed using the T-test or Mann-Whitney U-test, depending on the normality of the data. Correlations between analytes and laboratory parameters were also analyzed using Pearson or Spearman correlation, depending on the results of normality testing. Multigroup comparisons were performed using ANOVA, with Tukey post-hoc tests for normally distributed variables and Kruskal-Wallis tests and Dunn post-hoc tests for other variables. Statistical significance was set at $p<0.05$. The reliability of the correlation coefficients was checked using the Benjamini–Hochberg method. Statistical analyses were performed using GraphPad Prism 8.0.1 (GraphPad Software Inc., Boston, MA, USA).

4 Results

4.1 Comparison of stem cell mobilization strategies

4.1.1 Patient characteristics

During the 5-year study period, stem cell mobilization was performed in 210 patients. There was a slight male predominance (51.1%), and the average age was 61 years (range 32-75). 106 patients received a chemotherapy protocol for stem cell mobilization (chemomobilization group), while 104 patients received only G-CSF (solo G-CSF). The most frequently used chemotherapy mobilization protocol was cyclophosphamide monotherapy (84.9%), while a PACE-based combination protocol (15.1%) was used for the remaining patients. There were no differences in demographic, epidemiological, disease-related, or treatment parameters between the two groups receiving different mobilization strategies.

4.1.2 Efficacy of stem cell mobilization

In the Solo-G-CSF group, plerixafor was required significantly more often (45% vs. 13%, $p<0.001$) and stem cell mobilization was more frequently unsuccessful (11% vs. 3%, $p=0.024$). The mean number of stem cells collected was significantly lower (6.9 vs. 9.8 × 10^6/kg, $p<0.001$) compared to the chemomobilization group. However, the rate of infectious complications was lower (4% vs. 27%, $p<0.001$), as was the number of days spent in hospital (6 vs. 14 days, $p<0.001$). There was no significant difference in the median number of days of apheresis. Multivariate analysis identified the Cyto+G-CSF stem cell collection protocol as the only independent risk factor for infectious complications ($p=0.001$). The Solo-G-CSF protocol ($p<0.001$) and daratumumab exposure ($p=0.003$) predicted the need for subsequent plerixafor use. We found no independent prognostic factors for mobilization failure.

We also examined the effect of induction therapy on stem cell mobilization. Most patients received a bortezomib-based triple combination: VTD, VRd, and VCD. The number of stem cells collected was significantly lower in patients who received lenalidomide-containing treatment compared to patients who received induction therapy without lenalidomide (6.6 vs. 9.3 × 10^6/kg, $p<0.001$). In addition, the use of plerixafor was more common in patients receiving lenalidomide (40.8% vs. 23%, $p=0.007$). Furthermore, there was a noticeable but not significant difference in the rate of unsuccessful mobilization attempts (11.3% vs. 4.3%, $p=0.056$). However, lenalidomide exposure alone was not a predisposing factor for the use of plerixafor or mobilization failure. Eighteen patients received daratumumab prior to stem cell

collection, representing a relatively small proportion of the total patient population. Nevertheless, our data showed that daratumumab did not affect the efficiency of stem cell collection, but plerixafor was used more frequently in this patient group (77.8% vs. 24.5%, p<0.001).

4.2 Examination of biomarkers

4.2.1 Patient characteristics

The average age of patients was 69 years (range 39–81 years), with a slight male predominance (57.5%). The majority of patients received immunomodulatory agents (93%), proteasome inhibitors (95%), and dexamethasone (100%), while six (15%) patients received anti-CD38 monoclonal antibody therapy prior to sampling. The majority of patients were in remission (CR or VGPR) at the time of data collection, while six patients (15%) had progressive disease (PD).

4.2.2 Correlation with patient biological and disease characteristics

In order to obtain information on the potential applicability of serum adipokine levels as biomarkers, we examined how they relate to patient- and disease-specific prognostic markers already well known in MM. Age at sampling showed a positive correlation with chemerin (r=0.44, p=0.005), TSP-1 (r=0.39, p=0.012), and PON-1 (r=0.42, p=0.008) levels. These correlations remained significant after testing for false discovery rate (FDR) using the Benjamini-Hochberg method, confirming the close relationship between the markers studied and age in MM. No significant correlation was found between the concentrations of the other markers and gender, nor were there any gender differences in the laboratory parameters examined. When examining CRAB symptoms, we found that resistin levels were significantly lower in patients with renal failure than in patients without kidney disease (8752 vs. 5624 ng/mL, p = 0.003). Resistin levels were higher in patients with stage I R-ISS than in patients with advanced stages (R-ISS II-III) (10452 vs. 5842 ng/mL, p=0,032).

Among the various advanced stages of MM, resistin was able to differentiate with the following efficacy: within the CRAB criteria, resistin had high discriminatory potential between patients with and without renal failure (AUC 0.78, 95% CI 0.63–0.92), showing similar accuracy for patients with ISS stage I and ISS stages II–III according to the ISS staging system (AUC 0.71, 95% CI 0.54–0.89). Chemerin levels showed a positive correlation with B2MG levels (r=0.35, p=0.025), while TSP-1 showed a positive correlation with LDH (r=0.44, p=0.005). PON-1 showed a positive correlation with B2MG levels (r=0.85, p<0.001) and a negative correlation

with hemoglobin (r=−0.46, p=0.003) and GFR (r=−0.86, p<0.001). MPO showed a positive correlation with M protein (r=0.24, p=0.043) and serum albumin levels (r=0.41, p=0.009). Adiponectin, leptin, and adiponectin showed no significant correlation with LDH, albumin, B2MG, hemoglobin, or renal failure. None of the adipokine levels showed a significant correlation with hypercalcemia or the presence of bone lesions. There was no significant difference in marker levels between the cytogenetic risk groups determined by FISH, although the limited availability of genetic data made it difficult to detect statistical differences.

4.2.2.1 Correlation of adipokines with therapeutic response

Of the 40 patients, 5 (13%) were in CR, 26 (65%) in VGPR, 3 (8%) in SD, and 6 (15%) in PD at the time of sampling. When comparing response categories, we identified significantly lower adiponectin and TSP-1 levels in patients with PD than in patients with CR (41.5 vs. 130.3 µg/mL p=0.010 and 3307 vs. 5455 ng/mL, p=0.018).

4.2.2.2 Biomarker levels in the patient and control groups

Compared to the control, healthy population, MM patients had significantly higher mean adiponectin (77.5 vs. 52.1 µg/mL, p=0.003), resistin (9590 vs. 5471 ng/mL, p<0.001), chemerin (131 vs. 101 ng/mL, p=0.006), adiponectin (4.25 vs. 2.83 µg/mL, p<0.001), TSP-1 (4439 vs. 3261 ng/mL, p<0.001) and MPO (110 vs. 95 ng/mL, p=0.043) levels were measured. In contrast, leptin levels were higher in the control group (2.69 vs. 2.56 ng/mL, p=0.017). All seven differences remained significant after applying the Benjamini-Hochberg procedure. Overall, the ratio of mean adipokine levels in MM patients and controls was not significantly elevated (0.9–1.5), with the exception of resistin (1.8). There was no significant difference between patients and controls for PON-1. Based on ROC analysis, adiponectin (AUC = 0.78; 95% CI 0.67–0.88), TSP-1 (AUC = 0.78; 95% CI 0.67–0.88), and resistin (AUC = 0.76; 95% CI 0.65–0.86) showed the strongest discriminatory potential between MM patients and healthy controls. Adiponectin (AUC = 0.70; 95% CI 0.58–0.81), leptin (AUC = 0.67; 95% CI 0.55–0.80), chemerin (AUC = 0.64; 95% CI 0.52–0.77) and MPO (AUC=0.63; 95% CI 0.51–0.76) showed a more moderate but still significantly above-average accuracy in distinguishing between the groups.

5 Discussion

In recent decades, survival rates have improved significantly with the introduction of new drugs for the treatment of multiple myeloma. This raises the question of whether autologous stem cell transplantation is necessary even in young and fit patients when modern therapies are available.

Recent studies have clearly demonstrated that AHSCT following high-dose melphalan conditioning significantly improves progression-free survival, especially in patients with a poor prognosis. Therefore, international guidelines continue to recommend AHSCT in eligible patient populations. Although therapeutic outcomes have improved, the number of reliable prognostic markers for accurately predicting disease outcome remains limited. Currently widely used staging systems, such as ISS and R-ISS, are primarily based on laboratory parameters and cytogenetic abnormalities, but do not fully reflect the biological heterogeneity of MM. There is growing evidence that the bone marrow microenvironment, particularly adipocytes and the adipokines they produce, play a key role in plasma cell survival, drug resistance development, and disease progression, and may therefore form the basis for new prognostic approaches.

In the first part of our study, we analyzed the effectiveness of different stem cell mobilization strategies used in multiple myeloma. The method of stem cell mobilization depends on several factors, such as disease activity, the number of planned transplants, and the presence of risk factors predicting poor mobilization potential. Chemotherapy-based treatments involve the use of medium-dose cyclophosphamide, etoposide, cytarabine, or combination therapies. Cyto+G-CSF may be recommended for patients with active disease or who have previously undergone intensive treatment, as it is expected to result in more effective mobilization. Solo-G-CSF mobilization is associated with lower toxicity, as patients receive only colony-stimulating factor. Plerixafor, a selective and reversible CXCR4 inhibitor, can be added to the therapy if the primary mobilization proves ineffective. In some centers, it is used upfront, rather than only when necessary. Several studies have demonstrated the superiority of chemotherapy-based mobilization in terms of the number of stem cells collected and the number of successful attempts.

At our institute, G-CSF combined with medium-dose cyclophosphamide treatment has traditionally been the first-line treatment for stem cell mobilization. However, the 2020 coronavirus pandemic (COVID-19) forced us to change our strategy, as it became essential to avoid therapies associated with possible infectious complications and long hospital stays. As a result, starting in 2020, mobilization using the Solo-G-CSF protocol gradually became more common in our department than chemomobilization. Our goal was to retrospectively compare the effectiveness of the two mobilization techniques in our own MM patient population.

Half of our patients received chemotherapy, while the other half received only G-CSF. In the Cyto+G-CSF group, the collection procedure was more effective in terms of the number of stem

cells collected and the rate of unsuccessful attempts. Our results show that we can obtain a larger number of stem cells if we use chemotherapy in addition to G-CSF. However, it should be noted that despite the significant difference, both approaches resulted in the collection of a number of stem cells that significantly exceeded the minimum number required for AHSCT according to the IMWG guidelines. Not surprisingly, hospital treatment was significantly longer and infectious complications were more frequent in the case of Cyto+G-CSF. The frequency of infectious complications can be explained by the prolonged hospitalization itself, in addition to the immunosuppression caused by chemotherapy, and thus the exposure to nosocomial pathogens. With chemomobilization, only 13% of patients required plerixafor supplementation, compared with 45% in the Solo-G-CSF group. These results are consistent with data published in previous studies. Some data associate chemomobilization with higher costs due to longer hospital stays, while other studies suggest that the total cost of second-line, or "rescue mobilization," which is necessary due to the higher rate of plerixafor use and more frequent mobilization failure in strategies without chemotherapy, exceeds the financial burden of Cyto+G-CSF. Several studies support the idea that less plerixafor would be sufficient to achieve optimal stem cell counts.

We also examined the effects of induction therapies administered prior to stem cell collection. We have detailed knowledge of the negative effects of lenalidomide on stem cell mobilization. Our results are consistent with this experience, confirming that after prior use of lenalidomide, the number of stem cells collected was lower, the number of days spent in apheresis was higher, and the use of plerixafor was more frequent compared to lenalidomide-naive patients. However, in multivariate analysis, prior lenalidomide treatment was not found to be an independent predictive factor for either more frequent use of plerixafor or mobilization failure. Significantly less experience is available with daratumumab, which has only recently been included in the first-line therapies for transplant-eligible patients. Although daratumumab therapy is clearly beneficial in terms of depth of therapeutic response, progression-free survival, and overall survival, we have only limited data on the mobilization potential of patients pretreated with daratumumab. Chhabra S. et al. analyzed data on stem cell mobilization with Solo-G-CSF with or without upfront or on-demand use of plerixafor in a total of 291 patients who participated in the phase 2 MASTER and GRIFFIN studies. Both studies included patients treated with daratumumab-containing quadruplet therapy as first-line treatment, who collected fewer stem cells and required more apheresis attempts and plerixafor use compared to patients not receiving daratumumab treatment. The majority of patients studied in non-clinical trials experienced

reduced stem cell yield following daratumumab treatment, but two research groups reported similar efficacy when compared to patients who did not receive daratumumab treatment. Our own data showed that prior daratumumab treatment did not affect the success of stem cell collection, but significantly more frequent use of plerixafor was required to maintain the success rate, and the amount of stem cells collected was still lower than in patients who received daratumumab-free treatment. In addition to supporting previously published data, our results were the first to confirm in a multivariate analysis that prior daratumumab treatment is an independent predictor of plerixafor use during Solo-G-CSF mobilization. Using multivariate analysis, we were the first to demonstrate that in patients who received prior daratumumab treatment and were therefore immunosuppressed, the use of daratumumab did not represent an added risk of infectious complications during Cyto+G-CSF. Therefore, in this pretreated patient population, prior treatment with daratumumab should not influence our decision when considering the risk of infection in the choice of stem cell mobilization.

The use of venetoclax in MM is off-label, it has a favorable effect in cases with 11;14 translocation. To date, the effect of this agent on stem cell mobilization has not been studied. In our study, 5% of our patients received venetoclax treatment prior to mobilization, which, due to the low number of patients, did not provide sufficient statistical power to make significant conclusions, but based on our preliminary data, we cannot report any significant effect that would significantly impair mobilization.

In the other study, we measured the concentrations of circulating adipokines and certain related microenvironmental mediators in blood samples from patients treated for multiple myeloma. We explored their correlations with disease characteristics, treatment response, and clinical and laboratory markers. Our results provide further evidence that adipokine dysregulation is a relevant part of the pathobiology of MM. We were able to confirm that the kinetics of several molecules correlate significantly with various parameters indicating MM activity. These observations confirm that certain adipokines may function as potential biomarkers for MM and may serve as a basis for further clinical studies to clarify the role of adipokines in the development and progression of MM.

Adiponectin functions as a tumor-suppressive adipokine in MM, influencing the biology of plasma cells through metabolic and inflammatory signaling pathways. Experimental data suggest that adiponectin exerts its anti-myeloma properties through inhibition of the AKT and NFκB pathways. Comparing adiponectin levels measured in the preclinical stages of MM and

in manifest MM, they were found to be lower in smoldering and symptomatic MM than in MGUS. Higher pre-diagnostic adiponectin levels were associated with a lower risk of MM, particularly in the overweight population. Overall, adiponectin appears to have a protective effect against MM, with lower levels associated with higher risk, advanced disease profile, and more significant bone resorption. Contrary to previous epidemiological and preclinical data, we observed higher adiponectin concentrations in MM patients than in the healthy control group. This discrepancy may be due to differences in the stage of the patients we examined, therapy-related modulation of adipocyte function in treated patients, or the compensatory systemic response of tumor cells to metabolic stress, which heterogeneity can be partly attributed to the cross-sectional nature of our study. We believe that elevated adiponectin levels are an important factor in the modifying effect of treatment.

Leptin is a pro-inflammatory peptide hormone that regulates appetite and energy balance. Although most studies report elevated serum leptin levels in newly diagnosed MM, which may be associated with JAK/STAT and PI3K/AKT activation, we observed lower circulating levels in our patients. In addition, we found no correlation between leptin and other markers of disease. This result is consistent with previous findings that leptin concentrations decrease after treatment, which may be due to changes in metabolic status and accompanying changes in the chemokine profile. These results may also reflect catabolic states resulting from treatment-related weight loss, altered adipose tissue mass, or advanced disease, highlighting the complex interaction between systemic metabolism and MM biology.

Resistin, an adipokine associated with insulin resistance and inflammation, has been linked to MM risk based on the results of prospective studies. In addition to bone marrow adipocytes, it is also expressed by osteoblasts and osteoclasts, suggesting that it plays a role in the regulation of bone metabolism and bone remodeling. Based on the results of the largest meta-analysis, there is no difference in resistin levels between MM patients and healthy individuals. However, this observation is not consistent with the results of several prospective studies with low case numbers, which suggest that lower resistin levels, especially in men, may predispose to the development of MM, which can be explained by unregulated inflammatory signaling in the bone marrow microenvironment. The paradoxical decrease in resistin observed in patients with renal failure and advanced disease suggests that renal clearance and disease stage significantly influence circulating resistin levels. This complexity may explain the contradictions found in the literature and limits the applicability of resistin as an independent biomarker

Chemerin plays a key role in microenvironmental signaling through the regulation of immune cell chemotaxis and adipocyte differentiation. Data on chemerin in MM are limited, with only one retrospective analysis available from plasma samples from a randomized phase 3 clinical trial database. Chemerin concentrations were higher in patients than in healthy controls, and serum levels increased in parallel with R-ISS stage. In our MM population, chemerin levels showed a similar, significant difference compared to healthy controls. The confirmation of the correlation between chemerin and B2MG supports its role as a marker of tumor mass and thus disease activity, and is consistent with the observation that both molecules are sensitive markers of renal function deterioration.

Adipsin, also known as complement factor D, is a serine protease that plays a role in adipocyte cell biology, metabolic regulation, and activation of the alternative complement pathway. Adipocytes have been shown to activate autophagy and increase the expression of autophagy-related proteins, such as adipsin, thereby moderating chemotherapy-induced caspase activation and consequent apoptosis in abnormal plasma cells. Adipsin may also play a role in the development of bone involvement associated with MM, but it has not yet been investigated as a marker of the disease. Although our study confirms elevated levels of adipsin in MM, functional data remain limited. Given its role in complement activation and therapy resistance, further prospective studies are needed to determine whether adiposin directly contributes to tumor cell survival or bone involvement in vivo.

TSP-1 is the main regulator of TGF-β activation in the MM bone marrow microenvironment. Through modulation of TGF-β, TSP-1 may contribute to disease progression and serve as a biomarker. Although no prospective studies have examined TSP-1 levels in MM, its increased expression has been associated with poor prognosis in several other malignancies. Among our patients, TSP-1 levels were significantly higher in patients with MM than in the control group and showed a positive correlation with LDH, a marker of progressive disease. Our finding that lower TSP-1 levels indicate a poorer response to treatment may reflect its complex, bidirectional role in the biology of MM, where both excessive and decreased signaling may contribute to MM pathogenesis. This observation is consistent with the findings of Wu et al., who confirmed reduced TSP-1 synthesis in relapsed or refractory MM compared to newly diagnosed patients.

PON-1 contributes to the elimination of free radicals, influencing sensitivity to oxidative stress. A decrease in PON-1 activity has been demonstrated in chronic inflammatory conditions, but

its role in MM is not yet known. Based on a study conducted among Turkish patients, PON-1 levels were significantly lower in MM patients than in the control group, while no significant correlation was found between hemoglobin, creatinine, calcium, and albumin levels and PON-1. Plasma PON-1 levels tended to be lower in our MM patient population compared to the control group, but the difference was not statistically significant. However, the strong correlation between PON-1 and B2MG, hemoglobin, and renal function suggests that oxidative stress and systemic inflammation are closely related to MM activity. This supports the suggestion that PON-1 may serve as an indirect marker of metabolic stress in MM.

MPO, an oxidative enzyme expressed in myeloid cells, contributes to the response to oxidative stress, inflammation, and tissue injury, as well as to the modulation of the microenvironment. The development of MM is accompanied by increased production of MPO from myeloid cells, and under in vivo conditions, elevated levels of myeloid-derived MPO contribute to MM progression. In addition, increased MPO activity in the bone marrow microenvironment promotes plasma cell homing and tumor spread. Furthermore, MPO enhances the expression of genes promoting MM development in bone marrow stromal cells and inhibits tumor-specific T-cell response in vitro. Despite these observations, MPO has not yet been introduced as a biomarker in MM. In our MM population, MPO levels were higher than in the healthy control group and showed a positive correlation with serum albumin and M protein. Our results, in line with available preclinical data, suggest the existence of a mechanism whereby MPO may contribute to the development of a niche conducive to MM by promoting oxidative stress, suppressing antitumor immunity, and enhancing plasma cell migration. These findings add to the growing evidence that MPO is not only a passive participant but also an active contributor to the pathogenesis of MM.

Our results highlight the potential role of adipokines in the risk stratification of multiple myeloma. Markers such as chemerin, TSP-1, PON-1, resistin, and MPO correlate with tumor burden and disease activity, while adiponectin and TSP-1 correlate with response to treatment. These correlations suggest that adipokines may complement traditional markers (B2MG, LDH, albumin) in refining prognostic models and developing personalized therapeutic strategies. Overall, the collection of real-world data on biomarkers adds value to the treatment of MM. To the best of our knowledge, our study is the first to describe that adiponectin and resistin levels may increase due to MM treatment and that adipsin is a potential biomarker of disease activity, while TSP-1 levels in peripheral blood were significantly elevated compared to healthy controls.

6 New findings

1. We confirmed first in our multivariate analysis that prior daratumumab treatment is an independent predictor of plerixafor use during stem cell mobilization in MM.

2. Our multivariate analysis demonstrated first that in patients who received prior daratumumab treatment and were therefore immunosuppressed, the use of daratumumab did not represent an added risk of infectious complications during chemomobilization.

3. Our study was the first to demonstrate that adiponectin and resistin levels may increase as a result of MM treatment.

4. We were the first to highlight that adipsin may be a potential biomarker of disease activity.

5. Furthermore, we were the first to confirm that TSP-1 levels were significantly elevated in MM patients compared to healthy controls.

7 Summary

Multiple myeloma (MM) is a clinically and biologically highly heterogeneous malignant plasma cell disorder, the development and progression of which are driven by both genetic alterations and the complex interactions within the bone marrow microenvironment. Despite significant advances in the treatment of MM over recent decades, the disease remains incurable; therefore, the identification of novel prognostic biomarkers, as well as the optimization of therapeutic strategies, continues to be of major importance.

The present thesis addressed two main objectives. On one hand, it aimed to compare the clinical efficacy of different stem cell mobilization strategies in patients with MM eligible for autologous hematopoietic stem cell transplantation. Secondly, it sought to investigate the role of novel biomarkers associated with the bone marrow microenvironment and metabolic and inflammatory processes.

In the stem cell mobilization study, the effectiveness of stem cell collection using chemotherapy-based mobilization and granulocyte-colony stimulating factor (G-CSF) alone was analyzed. Our results demonstrated that the mobilization strategy significantly influenced the number of collected CD34+ cells, the number of apheresis procedures, the requirement for plerixafor, and overall mobilization success. At the same time, both approaches proved to be safe and clinically feasible.

In the biomarker analysis, serum levels of adipokines (adiponectin, leptin, resistin, chemerin, and adipsin), as well as other microenvironment-related proteins associated with oxidative stress and inflammation (thrombospondin-1, paraoxonase-1, and myeloperoxidase), were measured in patients with MM and in healthy control subjects. Several of the investigated biomarkers showed significant differences between the patient and control groups and were associated with biological characteristics of the disease and treatment response. The observed relationship between adipokines and the MM microenvironment highlights the pivotal role of metabolic and inflammatory mechanisms in the pathophysiology of the disease.

Overall, our findings underscore the potential prognostic relevance of biomarkers related to the bone marrow microenvironment and support the clinical rationale for a personalized approach to stem cell mobilization strategies in modern patient care.

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List of publications related to the dissertation

1. **Obajed Al-Ali, N.**, Csige, D., Pinczés, L. I., Farkas, K., Rebenku, I., Domján, A., Panyi, G., Szekanecz, Z., Szűcs, G., Illés, Á., Váróczy, L.: Adipokines as Prognostic Biomarkers in Multiple Myeloma: a Case-Control Study.
   Medicina (Kaunas). 61 (11), 1-13, 2025.
   DOI: http://dx.doi.org/10.3390/medicina61112065
   IF: 2.4 (2024)
2. **Obajed Al-Ali, N.**, Pinczés, L. I., Farkas, K., Kerekes, G., Illés, Á., Váróczy, L.: Steady-State Versus Chemotherapy-Based Stem Cell Mobilization in Multiple Myeloma: a Single-Center Study to Analyze Efficacy and Safety.
   J. Hematol. 13 (3), 79-85, 2024.
   DOI: http://dx.doi.org/10.14740/jh1256
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List of other publications

3. **Obajed Al-Ali, N.**: A normál hemostasis. Véralvadási tesztek.
   In: Hematológia. Szerk.: Gergely Lajos, Miltényi Zsófia, Váróczy László, Debreceni Egyetemi Kiadó, Debrecen, 213-224, 2025.
4. **Obajed Al-Ali, N.**: Paroxysmalis nocturnalis hemoglobinuria.
   In: Hematológia : Egyetemi jegyzet. Szerk.: Gergely Lajos, Miltényi Zsófia, Váróczy László, Debreceni Egyetemi Kiadó, Debrecen, 79-82, 2025.
5. **Obajed Al-Ali, N.**, Pinczés, L. I., Váróczy, L.: Myeloma multiplex és emlőcarcinoma társulása egy hazai hematológiai centrum adatai alapján.
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6. **Obajed Al-Ali, N.**, Tóth, S., Váróczy, L., Pinczés, L. I., Soltész, P., Szekanecz, Z., Kerekes, G.: One step back from bedside to the bench - How do different arterial stiffness parameters behave in relation to peripheral resistance?
   Diagnostics. 13, 1-14, 2023.
   DOI: https://doi.org/10.3390/diagnostics13182897
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7. Lovas, S., **Obajed Al-Ali, N.**, Varga, G., Szita, V., Alizadeh, H., Plander, M., Rajnics, P., Illés, Á., Szemlaky, Z., Mikala, G., Váróczy, L.: Pomalidomide Treatment in Relapsed/Refractory Multiple Myeloma Patients: Real-World Data From Hungary.
   Pathol. Oncol. Res. 28, 1-7, 2022.
   DOI: http://dx.doi.org/10.3389/pore.2022.1610645
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