SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

Our real-world clinical experience with daratumumab and pomalidomide in multiple myeloma

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1. Introduction

Multiple myeloma (MM) is characterized by clonal proliferation of abnormally transformed, plasma cells within the bone marrow. The WHO classifies MM as a mature peripheral B-cell neoplasm. MM accounts for about 2% of all cancers and is predominantly a disease of old age. The average age at diagnosis is 65 years. Male predominance is typical. The clinical manifestations of multiple myeloma are associated with either plasma cell expensionor abnormal accumulation of M-proteins (paraproteins) produced by them. Microscopic or flow cytometric examination of bone marrow samples is essential for diagnosis. The confirmation of genetic abnormalities is prognostically significant.

The treatment of multiple myeloma has evolved over the last 20 years, but it remains an incurable disease with alternating remissions and relapses.

The main goal of treatment is to achieve remission, prolong disease-free periods and survival, and maintain the best possible quality of life.

The combination of conventional cytostatic drugs, autologous stem cell transplantation and new therapeutic agents has improved the efficacy of therapy and increased overall survival (OS).

With the expansion of the treatment options, patients who were previously considered as refractory cases can achieve an adequate therapeutic response and treatment can be increasingly personalised by taking into account side effect profiles and comorbidities.

Novel knowledge about the treatment of MM is rapidly expanding due to a large number of new medicines. The results of clinical trials significantly influence therapeutic decisions, and choosing the right therapy is complicated by the different availability of drugs in different countries.

Currently, there are only limited 'real-world' data available on treatment in Hungarian clinical practice; therefore, in my work, I have retrospectively collected data from Hungarian haematology centres to investigate epidemiological data, clinical presentation, response to therapy, renal function and survival data.

2. Literature review

2.1. Pathogenesis

The management of multiple myeloma can be significantly improved by a better understanding of the pathogenesis of the disease, which is still the subject of research. The development of molecular biological modalities has confirmed that MM is a very heterogeneous disease, not only in clinical presentation and course but also genetically.

MM is classified on the plasma cell proliferative disorder's spectrum, including MGUS, smouldering (asymptomatic)MM, and MM (symptomatic). In all cases, the onset of the disease is preceded by an asymptomatic phase called MGUS (Monoclonal Gammopathy of Undetermined Significance), which remains undetected primarily. Approximately 10 per cent of cases are preceded by MGUS.

2.2. Genetic abnormalities

2.2.1. Primer genetic abnormalities

There are two types of primary genetic abnormalities, also known as disease-causing abnormalities. Hyperdiploidy, characterised by trisomy affecting the odd (chromosomes 3, 5, 7, 9, 11, 15, 19 and 21) chromosomes, is found in 50 per cent of patients. Regarding prognosis, patients in the hyperdiploid group typically have a better chance of survival and respond well to most treatments.

In the other half of patients, translocations affecting the immunoglobulin heavy chain (IgH) region develop, affecting the expression of the cyclin D, MMSET and MAF genes most frequently, with a female predominance. The five most frequently detected translocations are t (11,14), t (4,14), t (14,16), t (14,20), and t (6,14).

2.2.2. Other genetic abnormalities

The progression of MM accumulates newly acquired genetic abnormalities, leading to increased proliferation, genetic instability, and the emergence of therapy-resistant myeloma clones. Secondary abnormalities can manifest as DNA copy numbers, epigenetic alterations, and mutations (e.g., in RAS oncogenes).

Several signalling pathways have been investigated in genome sequencing, whose mutations may be activating or inhibitory but have in common the enhancement of malignant myeloma cell proliferation and survival.

2.3. Clinical characteristics

The suspicion of MM in everyday clinical practice may be raised by anaemia associated with renal failure and hypercalcaemia. The clinical manifestations of multiple myeloma are associated with plasma cell infiltration of various organs and bones and the abnormal accumulation of M-proteins (paraproteins) produced by them. The most common target organ lesions of this type, such as hypercalcaemia (28%), renal failure (48%), anaemia (73%) and lytic bone lesions (58%), are also known as CRAB symptoms. According to the literature, 60-70% of patients present with bone pain, most commonly in the lower back, and often after pathological fractures. In other cases, bone marrow insufficiency (anaemia, thrombocytopenia) or infections caused by immunosuppression are the leading symptoms, and skeletal abnormalities are absent. Renal failure is the first symptom in 10% of cases, with underlying hyperviscosity and plasma cell infiltration of the kidney. Only 1-2% of patients are confirmed to have extramedullary disease (EMD), during diagnosis.

2.4. Diagnosis

For the diagnosis of MM, bone marrow sampling (aspiration or biopsy) and May-Grünwald-Giemsa smear testing are mandatory. Traditionally, plasma cell proliferation above 10% has been considered abnormal, but the new IMWG criteria require that efforts be made to demonstrate the clonality of plasma cells.

Flow cytometry is a modern technique to distinguish between normal and abnormal plasma cells. It is also helpful in detecting the minimum residual disease (MRD). Myeloma cells have unique characteristics, bearing CD38, CD138, and CD56 antigens on the cell surface and showing CD19 and CD45 negativity. To determine the development and growth of myeloma cells, CD27 and CD117 labelling can be utilized.

A procedure called FISH is conducted on bone marrow samples to identify genetic abnormalities that are important for predicting outcomes but not essential for making a diagnosis.

Plasma cells produce an M-protein or free light chain, easily detected in serum or urine. In suspected cases of MM, agarose gel or capillary zone electrophoresis should be used as a screening method, and nephelometry and densitometric labelling are used for quantification. *Immunofixation* is a test that detects small amounts of M-component. In the case of multiple myeloma, serum paraprotein levels are typically above 30 g/l, with IgG and IgA types being the most common, while IgD, IgE, or IgM types are less frequent.

The traditional Bence-Jones test is the indirect detection of light chains in urine.

There are various imaging techniques available to detect bone lesions or plasmacytomas. X-ray examination is the most widely available method for confirming and following bone lesions. In 80% of newly diagnosed patients with myeloma, a bone lesion detectable by X-ray is already present; the most commonly affected bones are the vertebral column, ribs, skull, pelvis and long bones. New recommendations are increasingly focusing on modalities more advanced than X-rays. CT is more sensitive than X-rays, allowing the detection of minor bone defects and osseous and extraosseous plasmacytomas. Another imaging modality, MR scanning, provides an accurate picture of possible spinal cord and nerve compression, soft tissue involvement and infiltration of the bone marrow. PET-CT has a similar sensitivity to MR for detecting bone lesions but is less helpful in assessing bone marrow infiltration.

To establish the diagnosis of MM, the International Myeloma Working Group (IMWG) recommendation, introduced in November 2014, is used, which requires laboratory and imaging tests. Criteria for multiple myeloma, according to the IMWG recommendation, are

1. clonal plasma cell proliferation in the bone marrow (up to 10% or more) or solitary plasmacytoma,
2. Organ damage [summarised by the acronym CRAB: hypercalcemia (C), renal failure (R), anaemia (A), bone lesions (B)].
3. The latest IMWG recommendation includes three new factors: a ratio of plasma cells in bone marrow above 60%, a light chain ratio above 100, and more than one myeloma lesion as assessed by MRI.

2.5. Stage and risk classification

Nowadays, the survival of patients with MM still varies from a few months to a few decades, despite new treatment options. Staging can predict prognosis by considering tumour mass and other clinical features.

The International Staging System (ISS) was published in 2005 and is still commonly used. It is a simple system that applies to all newly diagnosed patients. Two parameters determine the staging of ISS: 1) beta-2-microglobulin levels, which indicate the size of the tumour mass, and 2) albumin levels, which indicate the patient's so-called fitness. Patients with MM can be categorized into three groups by disease severity, with significant differences in survival rates observed.

Risk stratification is essential for prognosis assessment and therapeutic decision-making and divides into two groups: high risk (t (4; 14), t (14; 16), t (14; 20), del17p13 or 1q amplification, elevated LDH level; bone marrow plasma cell above 20%) and standard risk (no previous abnormalities or t (11; 14), t (6; 14), hyperdiploid) MM. In order to assess the therapeutic response and the occurrence of relapse, it is necessary to perform status monitoring studies, which in clinical practice means the periodic determination of M-protein levels. Bone marrow sampling is necessary to confirm complete remission or minimal residual disease (MRD). In our national practice, flow cytometry measures MRD with a sensitivity level of 10^4, which is slightly below the 10^6 sensitivity level recommended in international recommendations (more sensitive flow cytometry, next-generation sequencing, mass spectrometry). Achieving MRD negativity indicates a favourable prognosis.

2.6. Treatment

The treatment of MM has developed dramatically in the last 20 years. Before 2000, the median survival of newly diagnosed MM patients was 2.5 years. Multiple myeloma is still an incurable disease, characterised by alternating remissions and relapses. First-line therapy can achieve complete remission, but relapse of the disease is still not preventable. It follows that the primary goal of treatment of multiple myeloma is to prolong survival while maintaining the best quality of life available.

The treatment strategy is determined by the course of the disease and the patient's general condition, age, and comorbidities. The primary decision is whether or not the patient is suitable for autologous stem cell transplantation following high-dose chemotherapy. In Hungary, according to the current professional recommendations, transplant-eligible MM patients (age younger than 70 years, without significant comorbidities) receive 3-4 cycles of induction therapy (mainly bortezomib-based triplet combinations) which is followed by stem cell collection and autologous haemopoietic stem cell transplantation. After that, maintenance therapy is necessary to prolong the remission phase as much as possible, for which the most accepted agent is lenalidomide currently. Previously, melphalan or cyclophosphamide protocols were utilized to treat patients deemed unsuitable for transplantation. According to the latest European recommendations, VRd or daratumumab-based combinations (DRd or D-VMP) are also recommended for patients unsuitable for transplantation. Unfortunately, these latter combinations are not available as first-line treatment in Hungary.

Over the past few years, the US Food and Drug Administration (FDA) has approved several treatments for relapsed MM, including carfilzomib, ixazomib, pomalidomide, elotuzumab, daratumumab, isatuximab, selinexor, belantamab mafodotin, and chimera antigen receptor T (CAR-T) cell therapy. The combination of conventional cytostatic agents, autologous stem cell transplantation and new therapeutic agents has improved the efficacy of therapy and increased overall survival (OS). The latest European recommendations also include an increasing number of new types of agents for treating newly diagnosed and relapsed cases. With the expansion of the therapeutic palette, patients who were previously poorly treated can achieve an adequate therapeutic response and treatment can be increasingly personalised by taking into account side effect profiles and comorbidities.

Knowledge about the management of MM is rapidly expanding due to many new drugs, but therapeutic decisions remain complicated by the different availability of drugs in international recommendations across countries.

2.7. New agents in the treatment of multiple myeloma

2.7.1. Immunomodulatory agents (IMiDs)

The first available immunomodulating drug was thalidomide more than 20 years ago, followed by the introduction of lenalidomide and pomalidomide as the next generations of the class.

All IMiDs have multiple effects including direct antitumour and specific immune responses, and they also inhibit myeloma cell growth via depleting bone marrow stromal cells and angiogenesis.

The first-generation IMiD, thalidomide, became the essential therapy for MM in the 2000s. However, its side effect of causing severe neuropathy led to a need for research into IMiDs with a more favourable side effect profile. In 2006, the FDA granted registration for lenalidomide, which is more effective and safer than its predecessor.

Pomalidomide is a third-generation IMiD approved by the FDA in 2013 for treating relapsed/refractory MM. The daily dose is 4 mg, but it may be gradually reduced to 1 mg. Half-life is 7.5-9.5 hours. As it is excreted via the liver and kidneys, dose reduction tailored to renal function is required. The main side effects include bone marrow failure, fatigue and diarrhoea.

2.7.2. Registration studies for pomalidomide

Numerous international clinical studies have investigated pomalidomide.

The MM03, also known as NIMBUS, was a clinical trial to study the efficacy and safe use of pomalidomide with the addition of low-dose (Pom/Dex) or high-dose (HDD) dexamethasone in patients who had previously received bortezomib and lenalidomide. As a result of the study, patients receiving Pom/Dex treatment had significantly better survival rates than those receiving HDD: median PFS 4 months vs 1.9 months and median OS 12.7 months vs 8.1 months. These differences are promising, but the highly pretreated patient group's expected survival remains low.

In another study of pomalidomide, the OPTIMISMM trial, the target population was MM patients who had received 1-3 prior lines of preventive therapy, including at least two cycles of lenalidomide-containing combination therapy. Seventy per cent of patients were lenalidomide-refractory. Patients received either pomalidomide-bortezomib-dexamethasone (PVd) triple therapy or bortezomib-dexamethasone (Vd) combination therapy. PVd significantly increased progression-free survival in the lenalidomide-refractory and non-refractory groups compared with the subgroup receiving Vd (12.0 and 22.0 months vs 5.59 and 9.53 months, respectively). The study observed that patients who had received a prior treatment cycle and were lenalidomide-refractory achieved a median progression-free survival of 17.84 months using PVd treatment compared to those receiving Vd treatment (9.49 months). Compared with Vd, patients receiving PVd treatment experienced better survival outcomes in several clinically essential subgroups: high-risk cytogenetic abnormalities (median 8.44 months vs 5.32 months) and prior proteasome-inhibiting therapy (median 10.91 months vs 6.31 months).

The introduction of monoclonal antibodies in treating relapsed/refractory multiple myeloma has opened up new possibilities for developing innovative pomalidomide-containing combinations.

The ICARIA study enrolled patients who had received at least two prior lines of therapy, including lenalidomide and a proteasome inhibitor. Patients received either isatuximab-pomalidomide-dexamethasone triple therapy or pomalidomide-dexamethasone therapy. During a median follow-up of 11.6 months, the median PFS was 11.5 months in the isatuximab+pomalidomide+dexamethasone group compared to 6.5 months in the pomalidomide+dexamethasone group. The results showed that the combination of pomalidomide and isatuximab provided a survival benefit in all specific subgroups, including patients with poor prognosis, lenalidomide refractoriness, prior proteasome inhibitor (PI) or lenalidomide+PI treatment.

2.7.3. Daratumumab

Daratumumab is a human monoclonal antibody type immunoglobulin G1 kappa (IgG1κ) that binds to CD38 and, in addition to direct antitumor activity, induces antibody-dependent cell-mediated cytotoxicity (ADCC) responses and complement-mediated tumour cell lysis. In addition to immune-mediated tumour cell killing, daratumumab enhances T-cell clonality, contributing to the clinical response through immunomodulatory effects. Several studies have confirmed that when combined with IMiDs, in particular lenalidomide, the antitumor effect of daratumumab can be enhanced. Currently, daratumumab is one of the most effective agents in treating relapsed/refractory MM (RRMM), which can be used in heavily pretreated patients, first as monotherapy and then in triple combination from the first relapse onwards.

2.7.4. Registration studies for daratumumab

The first monoclonal antibody used in multiple myeloma was daratumumab, introduced in the GEN501 and SIRIUS studies. Based on the pooled analysis of these two trials, the overall response rate (ORR) for heavily pretreated RRMM patients (more than five prior lines of therapy) was 31.1%, PFS was four months, and overall survival was 20.1 months. Subsequently, two pivotal clinical studies have demonstrated the extraordinary efficacy of daratumumab when used as part of combination therapy. In the CASTOR study, a triple regimen of daratumumab + bortezomib + dexamethasone (DVd) given to RRMM patients have compared to bortezomib + dexamethasone given in the control arm. After a median follow-up of 19.4 months, the overall response rate (83.8% vs 63.2%, $p<0.0001$) and progression-free survival (median 16.7 months vs 7.1 months, $p<0.0001$) of patients receiving the daratumumab-based combination were significantly better than those in the control arm. Patients treated with DVd showed better outcomes regarding side effect profile, lenalidomide refractory cases and cytogenetic status.

In POLLUX, patients received a combination of daratumumab + lenalidomide + dexamethasone (DRd) or lenalidomide + dexamethasone (Len/dex). After a median follow-up of 79.7 months, DRd treatment improved overall survival compared with the Len/dex group (median OS 67.7 months vs 51.8 months, $p<0.0044$). The overall response rate was 92.2% in the DRd subgroup and 76.4% in patients receiving Len/dex. The complete remission rate of patients who received DRd treatment was notably higher at 51.2% compared to the 21.0% rate observed in the Len/dex subgroup ($p<0.0001$). In daratumumab-based treatment subgroups,

PFS outcomes were more favourable in bortezomib-refractory cases prior to lenalidomide treatment and when adverse cytogenetic abnormalities occurred.

In the MAIA study, newly diagnosed MM patients ineligible for transplantation were treated with daratumumab+lenalidomide+dexamethasone (DRd) or lenalidomide+dexamethasone (Len/dex). After a median follow-up of 56.2 months, DRd treatment improved PFS compared to the Len/dex group (median not reached vs 34.4 months; $p<0.0001$).

ALCYONE also studied transplant-ineligible MM patients who received a combination of daratumumab+bortezomib+melphalan+prednisone (D-VMP) or bortezomib+melphalan+prednisone (VMP). After a median follow-up of 40.1 months, overall survival was significantly better in the D-VMP group.

The CASSIOPEIA study recruited newly diagnosed transplant-eligible MM patients from 111 European haematology centres, and patients have received treatment using either D-VTd (daratumumab + bortezomib + thalidomide + dexamethasone) or VTd (bortezomib + thalidomide + dexamethasone). The overall response rate was 29% in the D-VTd group and 20% in the VTd group. In APPOLLO, Daratumumab has been utilized in various combinations: patients received pomalidomide with CD 38 monoclonal antibody treatment. Inclusion criteria were: MRD-positive RRMM patients; those who received lenalidomide+PI in at least one prior line of therapy; those who achieved at least a partial response in 1 or more prior lines and those who were lenalidomide-refractory after at least one line of therapy. A subset of patients received either daratumumab + pomalidomide + dexamethasone or a combination of pomalidomide + dexamethasone, and further subgroups was formed based on the number of lines of therapy (1 vs 2-3 vs $\geq$4) and ISS staging (I vs II vs III). At a median follow-up of 16.9 months, the daratumumab+pomalidomide+dexamethasone group showed an improvement in progression-free survival compared to those treated with pomalidomide+dexamethasone (median 12.4 months [95% Cl 8.3-19.3] vs 6.9 months [5.5-9.3]; hazard ratio 0.63 [95% Cl 0.47-0.85] $p=0.0018$).

3. Aims

There are unmet needs to have comprehensive Hungarian data on treatment in clinical practice. We aimed to analyse 'real-world' data from patients with multiple myeloma. We analysed data on multiple myeloma from haematology centres in Hungary based on specific criteria:

1. To investigate the efficacy and safety of daratumumab-based treatments in relapsed/refractory MM patients.

2. To investigate the efficacy and safety of pomalidomide-based regimens in relapsed/refractory MM patients.

3. To search for correlations with epidemiological data, clinical presentation, disease severity, response to therapy, renal function, and survival data.

4. Patients and methods

Our retrospective studies analysed the clinical characteristics of patients treated for multiple myeloma with daratumumab and pomalidomide, from ten and six haematology centres in Hungary, respectively.

We collected data to examine the association between age, sex, clinical status, renal function, response to therapy and survival. We determined the ISS stage according the International Myeloma Working Group (IMWG) criteria. The design of the FISH assay was not uniform across the study centres, but the detection of del17p, t(11;14), t(4;14), t(14;16) and 1q 21 amplification mismatch was generally included. FISH results were considered unfavourable for confirmation of t (4;14), t (14;16), del17p and 1q21 amplification.

Patients received 16 mg/kg daratumumab intravenously once a week for the first eight weeks, followed by 16 mg/kg every two weeks (lenalidomide arm) or 16 mg/kg every three weeks (bortezomib arm) for 12 weeks, and finally 16 mg/kg every month. They received 20 mg dexamethasone per os (p.o.) or intravenously on days 1, 2, 4, 5, 8, 9, 11 and 12. The patients received Bortezomib (1-1.3 mg/m^2) on days 1, 4, 8, and 11 and Lenalidomide (10-25 mg/m^2) on days 1 and 2.

Pomalidomide was administered at a dose of 4 mg orally for days 1-21, in combination with 40 mg dexamethasone weekly as a doublet or, with the addition of a third agent, administered as a triplet. Patients received prophylactic anticoagulant treatment based on their risk factors and co-morbidities, including aspirin, small-molecule heparin, and vitamin K antagonists.

We assessed treatment response [complete response (CR), very good partial response (VGPR), partial response (PR), no response (NR) or progressive disease (PD)] and survival rates [progression-free survival (PFS), overall survival (OS)] according to the latest IMWG recommendations.

We defined overall survival (OS) as the time between the date of MM diagnosis and the last clinical data or the date of death. Progression-free survival (PFS) was calculated based on the time between diagnosis and confirmation of relapse or progression.

We performed statistical calculations using SPSS software versions 22.0 and 25.0. We compared survival times using Kaplan-Meier analysis and log-rank test. We considered differences significant if p was less than 0.05.

5. Results

3.1. Experiences with Daratumumab treatment

3.1.1. Patient characteristics

We analysed the data of patients treated in ten Hungarian haematology centres between September 2016 and December 2018 to investigate the use of daratumumab therapy. The 99 patients studied were gender-matched, with 51.1% being male. The mean age was 60.3 ± 10.7 (median: 62; range: 28-84). Patients were heavily pretreated, with a positional mean of 3 (range:1-12) for the prior lines of therapy. In terms of treatment, the majority of patients received bortezomib therapy (97%), with a large proportion also receiving lenalidomide (77.8%) and thalidomide (82.8%). Out of all the patients, 61 people (62.6%) underwent autologous hematopoietic stem cell transplantation (AHSCT). Before treatment with daratumumab, 63 patients had a FISH test. Of those, 36 patients (57.1%) had adverse cytogenetic abnormalities. The majority of patients were at high risk, according to ISS. We continued the treatment until progression, severe toxicity or death. The median positional number of prior treatment cycles was 5. Impaired renal function was found in 11 cases, six of which included haemodialysis.

3.1.2. Adverse events

Based side effects reported, daratumumab was well-tolerated, with few severe adverse reactions. The most frequently occurring adverse events included infusion-related reactions, haematological toxicities (mainly neutropenia), and infections.

3.1.3. Efficacy

Most patients (48 cases, 48.9%) received daratumumab monotherapy. Daratumumab was combined with bortezomib in 19 cases (19.3%) and lenalidomide in 29 cases. In three cases, we combined daratumumab with other agents (carfilzomib, cyclophosphamide). On average, patients who received daratumumab monotherapy had more prior lines of therapy than those who received lenalidomide-dexamethasone (DRd) or bortezomib-dexamethasone (DVD) triplets. Retrospectively, the average prior lines of therapy distribution were as follows: Dd:

4.13 ± 2.017; DRd: 3.58 ± 2.23; DVd: 2.77 ± 0.869. We evaluated the response to therapy in 88 patients: 12 complete (CR), ten very good partial (VGPR), 34 partial (PR), seven minor (MR) responses and 25 cases showed progression. In 9 patients, early death or short follow-up time did not allow an assessment of response. Patients receiving bortezomib or lenalidomide combination therapy had a significantly better response to treatment than those receiving monotherapy ($p<0.001$). Clinical follow-up continued until 31 December 2018. The median follow-up time was 18.6 (range:1-27.5) months, and the median progression-free survival (PFS) was 17.0 months. The median PFS of patients receiving lenalidomide combination therapy was better than that of the bortezomib combination group and those receiving monotherapy (6.6 months). The early-stage patients (ISS1) had significantly better survival than patients with more severe stages (ISS2, ISS3). The number of prior lines of therapy was also of great prognostic significance: heavily pretreated patients – those who received more than three lines of therapy – had worse PFS. Comparing FISH results, patients with adverse cytogenetic abnormalities showed worse survival outcomes than those with standard variations (post-ad hoc analysis, $p=0.133$). Analysing renal function parameters, survival data for patients with impaired renal function were not different from those with normal renal function.

3.2. Experiences with Pomalidomide treatment

3.2.1. Patient characteristics

Patient data from six haematology centres in Hungary, collected between July 2018 and December 2021, were used to investigate the use of pomalidomide therapy. Of the 86 patients studied, the sex ratio was considered balanced, with 55.8% male. The mean age at the start of pomalidomide treatment was 62.16 ± 8.7 (median: 62; range: 42-83). Patients were heavily pretreated, with a median of 4 (range: 2-12) prior lines of therapy. In terms of treatment, all patients received bortezomib or lenalidomide. Other previous therapeutic agents were daratumumab (57%), carfilzomib (39%), and ixazomib (28%). Furthermore, certain patients received treatment with novel and innovative medications.(isatuximab, venetoclax, selinexor, belantamab mafodotin). Of all the patients, 62.7% underwent autologous hematopoietic stem cell transplantation (AHSCT). Seventy-eight patients underwent FISH before pomalidomide treatment, of which 53 (61.6%) were confirmed to have an adverse cytogenetic abnormality. According to ISS, the majority of patients were at high risk. We found impaired renal function in 22 cases. Twenty-seven patients had extramedullary involvement at the beginning of

pomalidomide treatment. Extramedullary involvement was mainly confirmed using CT or MRI, while PET-CT was used in 8 cases.

3.2.2. Adverse effects

According incidence of adverse reactions recorded, pomalidomide was well-tolerated. Serious adverse events were reported relatively less frequently (38%). The most common adverse events were haematological toxicities (mainly neutropenia) and gastrointestinal adverse events (diarrhoea).

We observed ten fatal events, eight of which were pneumonia with associated sepsis and two severe haemorrhages. We confirmed COVID infection in 10 patients, two of which were fatal.

3.2.3. Efficacy

We treated most patients (45 cases, 52.39%) with dexamethasone alone and pomalidomide. In 38 cases (44.1%), pomalidomide was combined with a proteasome inhibitor (bortezomib, carfilzomib, ixazomib). We supplemented pomalidomide with other agents (daratumumab, venetoclax or pembrolizumab) in three cases. We continued treatment until progression, severe toxicity or death. Twenty-one patients with severe and moderate adverse events required a reduction in the starting dose. The median number of prior treatment cycles was 4 (2-12). Response rates were possible in all patients: 18% achieved a complete (CR) or very good partial (VGPR) response, and 38% achieved a partial (PR) response. The majority of patients treated with pomalidomide (44%) experienced only a minor response (MR) or a complete lack of response (no response-NR). Clinical follow-up lasted until 31 December 2021. The median follow-up time was 18.6 (range:1-30) months. The median progression-free survival (PFS) was 9.03 months, while the median overall survival was 16.53 months). Our results suggest that the median PFS was more favourable in patients receiving the proteasome inhibitor combination. Survival values for patients with early-stage (ISS1, ISS2) were significantly better than those with more severe stages (ISS3).

In our study, there was no significant difference between lenalidomide-refractory and non-refractory cases regarding the number of lines of prior therapy. Comparing the FISH results, patients with adverse cytogenetic abnormalities showed slightly or significantly worse survival outcomes than those with standard variations (post-ad hoc analysis, p=0.127). A study of renal function parameters showed that the survival of patients with reduced renal function was not

significantly different from that of patients with normal renal function. In patients with extramedullary manifestations, we observed significantly worse survival outcomes.

4. Discussion

Multiple myeloma is still an incurable disease, characterised by periods of remission and relapse. We can achieve a complete remission with first-line treatment, but relapse is inevitable. The main goal of treatment is to achieve remission, prolong the disease-free period and survival, and maintain the best possible quality of life.

The treatment of MM has rapidly developed during the last decades. The combination of conventional cytostatic drugs, autologous stem cell transplantation and new therapeutic agents has improved the efficacy of therapy and increased overall survival (OS). Expanding the therapeutic options has allowed for an adequate response in previously poorly treated patients and the personalisation of treatment by considering side effect profiles and comorbidities.
The knowledge about the treatment of MM is improving rapidly due to a large number of new therapies. The results of clinical trials significantly influence therapeutic decisions, and choosing the proper treatment can be challenging because drug availability varies among countries. Currently, only a limited amount of 'real-world' data is available on treating patients with multiple myeloma in clinical practice in Hungary. Therefore we aimed to collect data on treating patients with multiple myeloma with daratumumab and pomalidomide, including epidemiological data, clinical presentation, response to therapy, renal function and survival data.
In the literature, few publications discuss daratumumab treatment in real, everyday clinical practice. Minarik and colleagues (et al.) reported the results of 14 RRMM patients receiving heavily pretreated daratumumab monotherapy (median 4.5 prior lines of therapy). The overall response rate was 38%. The median PFS was 4.6 months, and median overall survival was not measured. Regarding side effects, we noticed primarily mild adverse events.
A French working group reported 41 studies of daratumumab monotherapy in RRMM patients in real-world clinical settings outside a clinical trial. Patients received a median of 4 prior lines of therapy, all of whom had received prior PI and Imid treatment and were refractory therapeutic agent immediately before daratumumab. The overall response rate was 24%; however, after 6.5 months of follow-up, all patients relapsed, with a median PFS of only 1.9 months. 99 RRMM patients had received daratumumab treatment in Hungary by December 2018.

Financial issues highly influenced our treatment decisions. Until June 2017, daratumumab was approved as monotherapy for heavily pre-treated patients (more than three lines of therapy) and was subsequently funded as a combination therapy after two lines of prior treatment.

In our study, most patients were heavily pretreated and received daratumumab monotherapy only, and their response and survival rates were comparable to those reported in the SIRIUS study. Although our patients received bortezomib and lenalidomide combination therapy, the response to therapy and survival outcomes were lower than those reported in the CASTOR and POLLUX studies. We explained differences because our patients were from the 'real world', so unlike the designed clinical trials, we did not relate the initiation of daratumumab treatment to strict criteria (ECOG status, renal function, blood count). In addition, our study treated fewer patients on 2nd and 3rd line therapy compared to the POLLUX and CASTOR studies. Analysis of subgroups showed that the number of ISS and prior lines of treatment were the most important predictive factors for survival. Survival outcomes of patients with adverse cytogenetic abnormalities were non-significant but lower than those with standard abnormalities. Interestingly, when we examined renal function parameters, the survival scores of patients with impaired renal function did not differ from those with normal GFR.

Given that in the POLLUX and CASTOR trials, daratumumab was not used in patients with impaired renal function. This study was the first in Hungary to show that daratumumab is safe in this subgroup.

In contrast to the registry studies, we observed more frequent serious adverse events, including death, in 14 cases (14.1%). Fortunately, most patients experienced only minor side effects or received treatment without complications.

Our study shows that daratumumab, the first monoclonal antibody registered in relapsed/refractory multiple myeloma, may be an effective and safely used therapeutic option in real-life clinical practice. However, the survival data and therapeutic outcomes are similar to the results of a selected patient population from formal clinical trials.

Our trial was the first Hungarian study to report real-life results for daratumumab monotherapy and combination therapy and showed that daratumumab could be used safely in renal failure.

Many studies have looked at the effectiveness of pomalidomide worldwide, but only a relatively small number of papers have published 'real world' data. A Japanese study group looked at data from 14 RRMM patients on pomalidomide treatment, which unfortunately showed that heavily pretreated patients did not tolerate pomalidomide well, and only 21.4% of patients were able to continue treatment for up to a year.

An Italian working group analysed data from 121 MM patients receiving Pom/Dex treatment in median line 4. The overall response rate was 43.3%, and the median PFS and median OS were 8.5 and 14 months, respectively.

Maciocia and colleagues collected data from five UK haematology centres and analysed data from seventy MM patients treated with pomalidomide between 2013 and 2016. Of these patients, 96.5% were refractory to immunomodulatory agents, 72.9% to IMiD and bortezomib, and 92.2% to the most recent line of treatment. The 28-day treatment cycle consisted of pomalidomide (daily on days 1 to 21), dexamethasone (days 1, 8, 15 and 22) plus/minus a third therapeutic agent. The overall response rate was 52.9%. Median follow-up was 13.2 months, median PFS was 5.2 months, and median overall survival was 13.7 months. We observed no significant differences regarding response, survival, renal function, age and cytogenetic abnormalities.

The Polish Charlinski and colleagues analysed 50 RRMM patients treated with pomalidomide+dexamethasone+ bortezomib or pomalidomide+dexamethasone. In the trial, the overall response rate was 39.1%. Median PFS and OS were 10.0 and 14.0 months, respectively. Regarding outcomes, there was no association between prior IMiD, bortezomib treatment or stem cell transplantation.

The Spanish PETHEMA-GEM working group investigated the efficacy of pomalidomide+cyclophosphamide+dexamethasone in RRMM patients. After analysing the survival data of 100 patients, the median PFS and OS were 7.6 months and 12.6 months, respectively, which we compared favourably with other triplets.

In a newer publication, US oncologists compared the efficacy of pomalidomide after second-line, prior lenalidomide-based treatment, using data from 300 RRMMs, 126 of whom received pomalidomide-based and 174 of whom received non-pomalidomide-based second-line treatment. The overall treatment response rates for the pomalidomide- and non-pomalidomide-treated groups were 78.6% and 51.7%, respectively ($p<0.0001$). The treatment response rate of pomalidomide-treated groups was 4.5-fold better. Median PFS was unmeasured in the pomalidomide group compared with 16.7 months in the non-pomalidomide group (log-rank $p<0.01$).

In Hungary, we treated 86 RRMM patients with pomalidomide by December 2021. NEAK funding significantly influenced our treatment decision, and most of our patients were heavily pre-treated and mainly treated with pomalidomide +/- dexamethasone +/- alkylating agent.

Interestingly, our results were more favourable than the MM03 study regarding therapeutic response and survival outcomes, similar to the results of the OPTIMISMM study and the Polish working group.
We observed more favourable PFS results in the patient group receiving the proteasome inhibitor-based combination. Our results showed that R-ISS and extramedullary manifestation were the most important predictive factors for survival. Patients with adverse genetic aberrations had significantly worse survival rates compared to the standard genetic aberration group.
Our results showed no significant correlation between the number of lines of therapy, lenalidomide refractoriness, and progression-free survival outcomes. Furthermore, when we examined renal function parameters, survival outcomes for patients with impaired renal function were interestingly not different from those with normal GFR. Our study was the first to demonstrate the safety of using pomalidomide in patients with impaired renal function, a group often excluded from clinical studies such as OPTIMISMM, ICARIA, and APOLLO.
As in the pivotal studies, 8 cases (9.3%) of serious adverse events, including death, were observed. Fortunately, many patients experienced only minor side effects or received treatment without complications.

The limiting factor of our studies is the retrospective, multicentre data collection, which implies a lack of knowledge of the medical history of some patients.

In our two Hungarian data collections, patients' demographic and clinical characteristics were in line with the international literature. Based on these findings, our patient database reflects the real-world experience of routine patient care. It complements the results of selected patient populations from clinical trials, thus representing the principal value of this work.

5. New findings

1. Innovative agents, like the first anti-CD-38 monoclonal antibody daratumumab and the immunomodulatory pomalidomide, can be effectively used in clinical practice in relapsed/refractory MM.

2. In our 'real world' data analyses, daratumumab and pomalidomide had a favourable side effect profile, with serious side effects being infrequent.

3. Both agents can be used safely in patients with normal or impaired renal function.

4. Our analyses showed that the number of prior lines of therapy, higher risk group (ISS3) and adverse cytogenetic variation were of prognostic significance.

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7. Publications

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Registry number: DEENK/204/2023.PL
Subject: PhD Publication List

Candidate: Szilvia Lovas
Doctoral School: Doctoral School of Clinical Medicine
MTMT ID: 10064325

List of publications related to the dissertation

1. **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.
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DOI: http://dx.doi.org/10.3389/pore.2022.1610645
IF: 2.874 (2021)

2. **Lovas, S.**, Varga, G., Farkas, P., Masszi, T., Wohner, N., Bereczki, Á., Adamkovich, N., Borbényi, Z., Szomor, Á., Alizadeh, H., Szaleczky, E., Wolf, K., Schneider, T., Plander, M., Szendrei, T., Csacsovszki, O., Csukly, Z., Rajnics, P., Egyed, M., Nagy, Z., Rejtő, L., Illés, Á., Mikala, G., Váróczy, L.: Real-world data on the efficacy and safety of daratumumab treatment in Hungarian relapsed/refractory multiple myeloma patients.
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