





Optimization of treatment of patients with plasma cell myeloma with high cytogenetic risk in Poland

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Abstract

Plasma cell myeloma (PCM) is a hematologic malignancy that derives from mature B cells. The prognosis of patients with PCM is highly dependent on the presence of cytogenetic aberrations. Determination of cytogenetic risk enables informing patients about their prognosis and allows for individual choice of therapy. In Poland, cytogenetic risk assessment is a fully reimbursed procedure, and it is recommended to perform such an examination in every diagnosed patient. Therapy of patients with high cytogenetic risk should be planned with consideration of tandem autotransplantation of hematopoietic cells in eligible patients. In patients with refractory or relapsed PCM, treatment with ixazomib in combination with lenalidomide and dexamethasone appears to remove cytogenetic risk.

Key words: multiple myeloma, plasma cell myeloma, refractory multiple myeloma, relapsed multiple myeloma, cytogenetic risk, therapy

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Introduction

Plasma cell myeloma (PCM) is a malignant haematological neoplasm derived from mature B cells. After recombination of the heavy chain class, immunoglobulins produce a monoclonal (M) protein, which is deposited in the bone marrow and internal organs, causing disease symptoms [1].

Multiple myeloma accounts for 1–2% of all neoplasms and 18% of haematological malignancies. In 2018, 1,583 new cases of PCM were registered in Poland, but this number is underestimated, considering more than 2,000 new cases reported annually to National Health Fund (NFZ, *Narodowy Fundusz Zdrowia*) for settlement benefits [1, 2]. The dis-

ease mainly affects the elderly — the median age at diagnosis is 65–70 years. Over 90% of patients are over 50. According to the American Society of Clinical Oncology (ASCO) data, the 5-year survival rate in PCM patients is approximately 54% [3].

The aetiology of PCM has not been fully understood; environmental exposure and genetic predisposition play a significant role in the development of the disease. The disease course varies greatly, with a typical symptom including bone pain caused by osteolytic lesions that can lead to pathological fractures. The progressive infiltration of pathological plasma cells may cause frequent infections, anaemia, renal failure, peripheral neuropathy and venous thromboembolism [4, 5].

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Table 1. SLiM CRAB criteria for end-organ damage related to multiple myeloma (source [4])

C (calcium)	Hypercalcemia, corrected serum calcium level > 0.25 mmol/L (> 1 mg/dL) above the upper reference limit or > 2.75 mmol/L (11 mg/dL)
R (renal insufficiency)	Creatinine clearance < 40 mL/min or serum creatinine > 173 μmol/L (2 mg/dL)
A (anemia)	Hemoglobin 2 g/dL below the lower reference value or < 10 g/dL
B (bones)	Osteolytic lesions in bone radiography, computed tomography or positron emission tomography
S (sixty)	Clonal plasma cells in the bone marrow greater than or equal to 60%
Li (light chains)	Involved/uninvolved free light chain ratio of 100 or more
M (magnetic resonance)	More than one focal marrow lesion

Table 2. Diagnostic criteria for multiple myeloma and the conditions preceding the disease (based on [6])

MGUS, monoclonal gammopathy of undetermined significance	SMM, smoldering multiple myeloma	PCM, plasma cell myeloma
M protein serum level < 3 g/dL	M protein serum level ≥ 3 g/dL or ≥ 500 mg/day in 24-hour urine collection	Presence of M protein in serum or urine
Clonal plasma cells in the bone marrow below 10%	Clonal plasma cells in the bone marrow below 10–60%	Clonal plasma cells in the bone marrow ≥ 10%
No SLiM CRAB criteria met and no amyloidosis	No SLiM CRAB criteria met and no amyloidosis	≥1 SLiM CRAB criteria met

Diagnosis

PCM typically begins with a precancerous condition referred to as monoclonal gammopathy of undetermined significance (MGUS). It is characterized by the absence of clinical signs and symptoms, but already at this stage, there are plasma cell dysfunctions. The risk of progression from MGUS to PCM is estimated at 1.5% per year and increases with age [4].

The intermediate state between MGUS and PCM is smoldering multiple myeloma (SMM). Like MGUS, the condition is asymptomatic, but the M protein serum level and the percentage of clonal plasma cells in the bone marrow are higher. Smoldering multiple myeloma occurs in about 8% of patients, and the risk of progression to PCM is 51% within 5 years of diagnosis and increases to 66% after 10 years and 73% after 15 years, respectively [4].

The diagnosis of PCM is based on the presence of clonal plasma cells in the bone marrow identified with the use of immunophenotyping or immunohistochemistry of bone marrow trephine biopsy (BMT) specimen. Another criterion for PCM diagnosis is the presence of at least one symptom of end-organ damage according to the SLiM CRAB criteria (Table 1) [4, 6]. The criteria for PCM diagnosis and the preceding conditions are presented in Table 2.

Prognostic factors in multiple myeloma

At each stage of PCM development, prognostic factors can be distinguished and the risk of transformation into symptomatic myeloma can be determined. Risk factors for the transformation of MGUS into the treatment requiring disease include [7]:

- serum M protein above 1.5 g/dL;
- presence of aberrant plasma cells in the bone marrow;
- polyclonal suppression of immunoglobulins;
- non-IgG subtype;
- abnormal free light chains serum level;
- cytogenetic aberrations;
- DNA aneuploidy;
- circulating plasma cells;
- single bone lesions visible on magnetic resonance or positron emission tomography.

The available prognostic model of the 20-year progression of MGUS to PCM takes into account three major risk factors, i.e. M protein level above 1.5 g/dL, non-IgG subtype, and abnormal free light chains serum level. The absence of any of these factors was associated with a 5% risk of progression to PCM over 20 years. The presence of one factor increased the risk of progression to 21% of two factors to 37%, and of three factors to 58% [8].

Mayo Clinic and PETHEMA models help determine the risk of progression from SMM to

Table 3. Risk stratification of progression in smoldering multiple myeloma (based on [6])

Number of risk factors	Risk of 5-year progression (%)
According to the Mayo Clinic model	
1	25
2	51
3	76
According to the PETHEMA model	
1	4
2	46
3	72

PCM. The former analyses the presence of three risk factors, such as the percentage of plasma cells in the bone marrow greater than or equal to 10%, serum M protein exceeding 3 g/dL and kappa free light chains/lambda free light chains serum concentration ratio lower than 0.125 or greater than 8. The prediction of progression in the PETHEMA model is based on the flow cytometry analysis of bone marrow aspirate. The presence of not less than 95% of abnormal plasma cells and polyclonal immunoglobulin suppression (immunoparesis) increase the risk of progression [6]. Table 3 presents progression risk assessed using Mayo Clinic and PETHEMA model.

Disease stage analysis and identifying PCM prognostic factors are of key importance in the prognosis assessment and are the basis for determining the appropriate therapy.

The PCM risk factors can be divided into patient- and tumour biology-related. Patient-related parameters include age over 75 years and poor performance status. The basis of the International Staging System (ISS) and its latest modification Revised International Staging System (R-ISS) are factors related to cancer biology; they precisely define PCM prognostic categories. The R-ISS considers the biochemical parameters captured by the ISS as well as the presence of significant cytogenetic aberrations and lactate dehydrogenase (LDH) levels (Table 4) [9].

Cytogenetic diagnostics

The prognosis of PCM patients largely depends on the presence of cytogenetic aberrations. The determination of cytogenetic risk enables the patients to be informed about the prognosis and allows therapy personalization. There are two main groups of cytogenetic aberrations: the hyperdiploid type associated with a good prognosis and with accompanying trisomies of odd-numbered chromosomes, and the aggressive non-hyperdiploid type characterized by translocation in immunoglobulins encoding genes. The fluorescent *in situ*

Table 4. Prognostic classification in multiple myeloma based on the International Staging System (ISS) and the Revised International Staging System (R-ISS) criteria (based on [9])

Stage	Parameter	Median survival time (months)
ISS		
ISS 1	<ul style="list-style-type: none"> Serum β_2-microglobulin < 3.5 mg/L Serum albumin \geq 3.5 g/dL 	62
ISS 2	<ul style="list-style-type: none"> Serum β_2-microglobulin < 3.5 mg/L Serum albumin < 3.5 g/dL or serum β_2-microglobulin 3.5–5.5 mg/L 	44
ISS 3	<ul style="list-style-type: none"> Serum β_2-microglobulin > 5.5 mg/L 	29
R-ISS		
		5-year survival rate (%)
R-ISS 1	<ul style="list-style-type: none"> Serum β_2-microglobulin < 3.5 mg/L Serum albumin \geq 3.5 g/dL No high-risk cytogenetic aberrations Normal LDH activity 	82
R-ISS 2	<ul style="list-style-type: none"> R-ISS 1 and R-ISS 3 criteria not met 	62
R-ISS 3	<ul style="list-style-type: none"> Serum β_2-microglobulin > 5.5 mg/L Presence of cytogenetic aberrations: del(17p) and/or t(4;14), and/or t(14;16) or LDH activity above normal 	40

LDH — lactate dehydrogenase

Table 5. Cytogenetic risk groups according to Intergroupe Francophone du Myelome (IFM) and Mayo Clinic [10, 11]

High risk	Intermediate risk	Standard risk
<ul style="list-style-type: none"> • Unfavorable signature in gene expression profile • del(17p) • t(14;16) determined by the FISH method • t(14;20) 	<ul style="list-style-type: none"> • del(13q) determined by the cytogenetic method • Hypodiploidy • t(4;14) determined by the FISH method 	<ul style="list-style-type: none"> • t(11;14) • t(6;14) • Hyperdiploidy

FISH — fluorescent *in situ* hybridization

hybridization (FISH) offers the possibility of a specific assessment of plasma cell abnormalities. Detection of specific aberrations in bone marrow plasma cells allows for the allocation of patients to one of the three cytogenetic risk groups (Table 5). Genetic disorders occur in approximately 80% of PCM patients, while a high cytogenetic risk is observed in 15–20% of patients. The unfavourable prognosis is related to the presence of del17p and t(14; 6), t(14;20), t(4;14) [10–12].

In Poland, the NHF reimburses cytogenetic tests. Therefore, the assessment of cytogenetic risk should be performed on every diagnosed patient before treatment initiation.

It should be remembered that to qualify a patient for treatment with ixazomib in combination with lenalidomide and dexamethasone under the drug program, it is necessary to document the presence of del(17p) or t(4;14) or t(14;16) [13].

In a recent survey conducted among 96 PCM patients in Poland, 64.6% of respondents indicated that they know what a genetic test is. Half of the patients (50%) declared that they had such tests performed [14].

The algorithm developed by the Polish Myeloma Group allows for quick detection of cytogenetic aberrations with the greatest impact on treatment (Figure 1) [4].

A cytogenetic risk assessment by FISH should be performed on every patient with a confirmed PCM diagnosis using at least a minimal set of DNA probes.

Treatment of multiple myeloma in patients at high cytogenetic risk

Currently, the first step of management in patients eligible for autologous hematopoietic stem cell transplantation (auto-HSCT) is remission induction therapy. Preferred induction protocols include bortezomib-based triple combination therapies:

- VTd — bortezomib, thalidomide, dexamethasone;

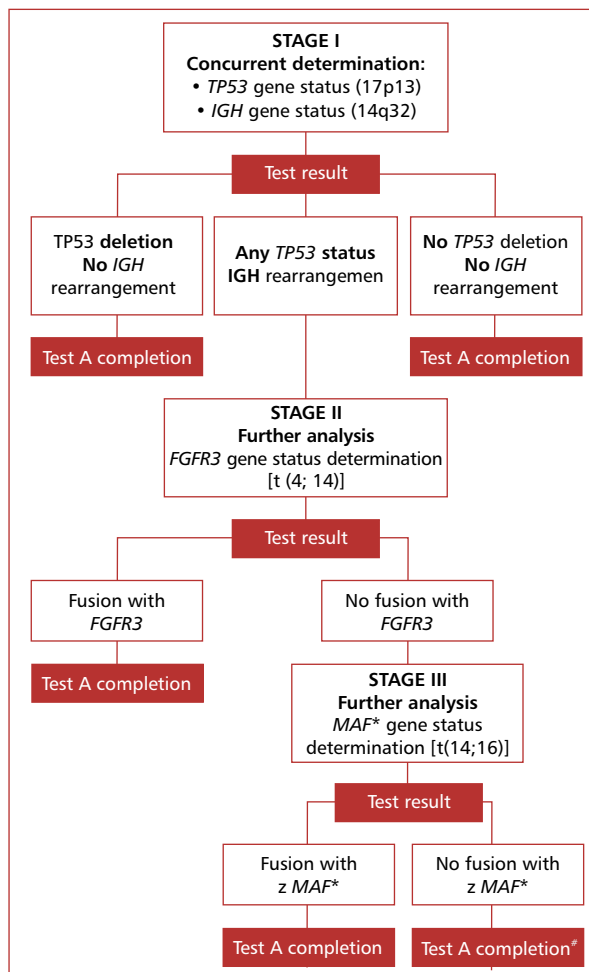


Figure 1. Basic test by the fluorescent *in situ* hybridization (FISH) method with the use of a minimal set of DNA probes (algorithm prepared by the Polish Myeloma Group [4]); # possible to perform an extended test to identify an *IGH* translocation partner; *synonyms used: *MAFC*, *c-MAF*

- VCd — bortezomib, cyclophosphamide, dexamethasone;
- PAD — bortezomib, doxorubicin, dexamethasone;
- CTD — cyclophosphamide, thalidomide, dexamethasone.

Tandem auto-HSCT can be performed in patients at high cytogenetic risk. The results of some clinical trials indicate the advantage of this approach over single transplantation. In a study by Cavo et al. [15], median progression-free survival (PFS) and overall survival (OS) were significantly higher in patients undergoing the tandem transplantation procedure [15]. The results obtained by Gagelmann et al. [16] showed that performing tandem transplantation eliminates the cytogenetic risk in PCM patients.

According to the drug program, in the case of the first relapse, the second line treatment includes the following regimens [4, 13]:

- Kd — carfilzomib, dexamethasone;
- KRd — carfilzomib, lenalidomide, dexamethasone (in the case of no response to bortezomib in auto-HSCT eligible patients);
- DvD — daratumumab, bortezomib, dexamethasone (in the case of relapse after auto-HSCT in patients with good response to bortezomib);
- Rd — lenalidomide, dexamethasone (in patients with peripheral polyneuropathy).

As shown in the ASPIRE study, treatment according to the KRd regimen improves but does not eliminate the poor prognosis associated with high cytogenetic risk. In patients at high cytogenetic risk treated with the KRd regimen, a higher median PFS (23.1 months) was observed compared to those treated with the Rd regimen (13.9 months), however with no statistical significance [17].

In the ENDEAVOR study, patients at high cytogenetic risk treated with the Kd regimen had a higher median PFS (8.8 months) and OS (28.0 months) compared to patients treated with the Vd regimen (bortezomib and dexamethasone), with median PFS and OS of 6.0 months and 22.7 months, respectively [18, 19].

In the CASTOR study, in patients at high cytogenetic risk treated with the DvD regimen, median PFS was higher (12.6 months) than in those treated with the Vd regimen (6.2 months). A higher median PFS was observed in patients who were treated for the first relapse and was 20.1 months for the DvD regimen and 8.4 months for the Vd regimen, respectively [20].

According to the drug program, in the case of subsequent relapses, the third and fourth treatment lines include the following protocols [4, 13]:

- iRd — ixazomib, lenalidomide, dexamethasone (no resistance to lenalidomide in patients at high cytogenetic risk);
- Kd;
- Rd;

- DVd (patients previously treated with bortezomib and lenalidomide);
- Pd — pomalidomide, dexamethasone (patients previously treated with bortezomib and lenalidomide);
- KRd (no response to bortezomib or progression in response to lenalidomide in patients eligible for auto-HSCT);
- PVd — pomalidomide, bortezomib, dexamethasone (patients previously treated with lenalidomide with no contraindications to bortezomib use).

Treatment with a Pd regimen does not completely eliminate the cytogenetic risk in patients with relapsed, refractory PCM. In the study by Dimopoulos et al. [21], the median PFS in patients at standard cytogenetic risk was 4.2 months. For comparison, the median PFS in the group of patients with del(17p) was 4.6 months, and with t(4;14) — 2.8 months. Overall survival in patients at standard cytogenetic risk was 14.0 months, the presence of del(17p) reduced the median OS to 12.6 months, and the presence of t(4;14) — to 7.5 months [21].

The TOURMALINE study, comparing iRd and Rd regimens, deserves special attention. The median PFS in patients at high cytogenetic risk treated with the iRd regimen was 21.4 months versus 9.7 months in patients treated with the Rd regimen. Median PFS in patients at standard cytogenetic risk receiving iRd was 20.6 months compared with 15.6 months in patients treated with the Rd regimen. The results of this study lead to the conclusion that adding ixazomib to the Rd regimen reduces the cytogenetic risk in PCM patients [22]. Figure 2 summarizes the therapeutic options in patients with PCM eligible for auto-HSCT.

The prognosis of patients at high cytogenetic, not eligible for auto-HSCT is much worse than that of patients at standard risk. It is estimated that the presence of t(4;14) reduces the median PFS and OS almost twice, while the presence of del(17p) — more than twice [23]. According to the drug program, the first-line treatment of patients not eligible for auto-HSCT is based on the following protocols [4, 13]:

- VMP — bortezomib, melphalan, prednisone;
- Vcd — bortezomib, cyclophosphamide, dexamethasone;
- VTd — bortezomib, thalidomide, dexamethasone;
- VRd — bortezomib, lenalidomide, dexamethasone;
- Rd — lenalidomide, dexamethasone (should not be used in patients at high cytogenetic risk).

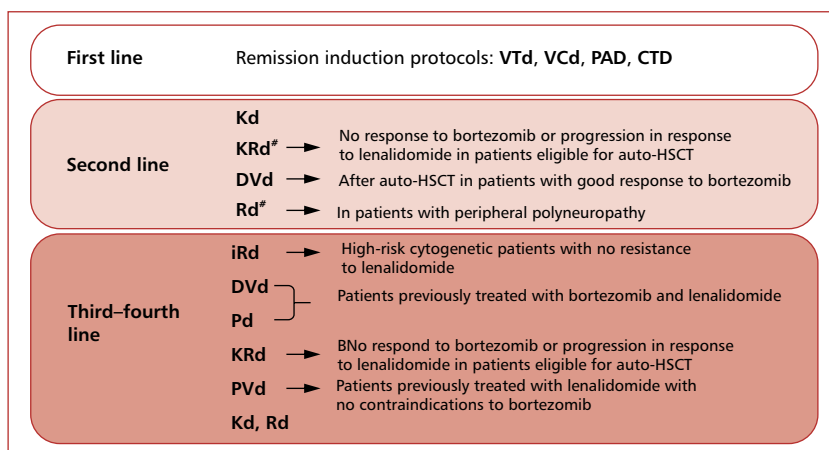


Figure 2. Therapeutic management in patients with multiple myeloma eligible for hematopoietic stem cell transplantation (based on [4, 13]); auto-HSCT — autologous hematopoietic stem cell transplantation; CTD — cyclophosphamide, thalidomide, dexamethasone; DVd — daratumumab, bortezomib, dexamethasone; iRd — ixazomib, lenalidomide, dexamethasone; Kd — carfilzomib, dexamethasone; KRd — carfilzomib, lenalidomide, dexamethasone; PAD — bortezomib, doxorubicin, dexamethasone; Pd — pomalidomide, dexamethasone; PVd — pomalidomide, bortezomib, dexamethasone; Rd — lenalidomide, dexamethasone; VCd — bortezomib, cyclophosphamide, dexamethasone; VTd — bortezomib, thalidomide, dexamethasone; #protocols not recommended in the case of planned treatment according to the iRD regimen

According to the drug program, in the case of the first relapse, the second line treatment includes the following regimens [4, 13]:

- KD;
- PVd (patients previously treated with lenalidomide with no contraindications to bortezomib use);
- Rd (patients with peripheral polyneuropathy or when bortezomib was used as first-line treatment).

According to the drug program, in the case of subsequent relapses, the third and fourth treatment lines include the following protocols [4, 13]:

- Kd;
- Rd;
- DVd (patients previously treated with bortezomib and lenalidomide);
- Pd (patients previously treated with bortezomib and lenalidomide);
- iRd (no resistance to lenalidomide in patients at high cytogenetic risk);
- PVd (lenalidomide-treated patients with no contraindications to bortezomib use).

Figure 3 presents the therapeutic options for PCM patients not eligible for auto-HSCT.

Summary

Multiple myeloma is an extremely heterogeneous disease, with the prognosis influenced by

environmental and cancer biology-related factors. The determination of cytogenetic risk in patients with PCM influences the choice of treatment method and allows patients to be informed about the prognosis. In Poland, the NHF reimburses cytogenetic tests, therefore it is recommended to assess the cytogenetic risk in each diagnosed patient before treatment initiation. Nevertheless, the number of cytogenetic tests performed in Poland seems to be insufficient. The high cytogenetic risk significantly reduces therapy effectiveness. Tandem hematopoietic stem cell transplantation and treatment according to iRD protocol reduce cytogenetic risk in PCMM patients.

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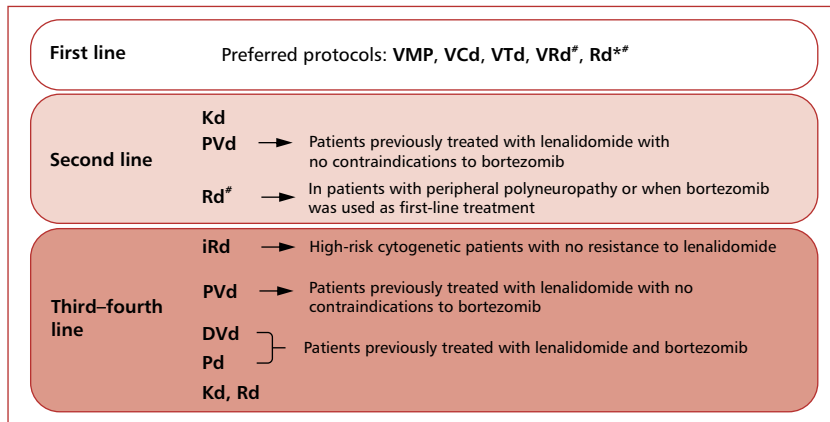


Figure 3. Therapeutic management in patients with multiple myeloma not eligible for hematopoietic stem cell transplantation (based on [4, 13]); DvD — daratumumab, bortezomib, dexamethasone; iRd — ixazomib, lenalidomide, dexamethasone; Kd — carfilzomib, dexamethasone; Pd — pomalidomide, dexamethasone; PVd — pomalidomide, bortezomib, dexamethasone; Rd — lenalidomide, dexamethasone; Rd — lenalidomide, dexamethasone; VCd — bortezomib, cyclophosphamide, dexamethasone; VMP — bortezomib, melphalan, prednisone; VRd — bortezomib, lenalidomide, dexamethasone; VTd — bortezomib, thalidomide, dexamethasone; *should not be used in the case of high cytogenetic risk; #protocols not recommended in the case of planned treatment according to the iRD regimen

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