

Original article

Impact of CD56 Expression on Plasma Cells in Patients with Newly Diagnosed Multiple Myeloma

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Abstract

Background. Multiple myeloma (MM) is a heterogeneous hematologic malignancy with variable clinical course and response to therapy [1,2]. Unfortunately, MM is still an incurable disease, and the difference in overall survival (OS) and progressive free survival (PFS) rates in patients varies depending on the risk group. Due to the limited access to high-tech molecular genetic studies for risk group stratification, it remains relevant to study more accessible prognostic markers, in particular based on flow cytometry data [1,8].

Aim. In our study, our goal was to evaluate the level of CD56 expression on pathological plasma cells and their effect on the frequency of objective response to induction therapy and overall survival rates in patients with newly diagnosed MM.

Materials and Methods. We conducted a retrospective single-center analysis of 26 newly diagnosed MM patients treated at the National Research Oncology Center in

Astana, Kazakhstan. For immunophenotyping of plasma cells, we employed multicolor flow cytometry following the standardized EuroFlow protocol with its recommended antibody panels [7,17]. Only patients with $\geq 10\%$ clonal plasma cells and an aberrant immunophenotype were included, in accordance with international recommendations [4,7,13]. Patients were stratified according to CD56 expression level. All patients received VCD induction therapy. Response was evaluated according to IMWG criteria, and OS was analyzed using Kaplan–Meier curves [3,11]. **Results.** High objective response rates and 100% overall survival at 24 months were observed in patients with CD56 expression $\leq 30\%$, while patients with negative CD56 expression and those with CD56 expression $>30\%$ were more likely to experience primary refractoriness and a tendency toward lower overall survival. However, in our study, the differences did not reach statistical significance ($p=0.31$), possibly due to the limited patient sample, but we do see a trend toward worse outcomes. **Conclusion.** CD56 expression is an accessible additional prognostic marker and may be used for treatment personalization in patients with multiple myeloma.

Keywords: multiple myeloma, CD56, flow cytometry, immunophenotyping, prognosis.

1. Introduction

Multiple myeloma (MM) is a malignant plasma cell disease characterized by clonal proliferation of bone marrow plasma cells, production of monoclonal immunoglobulin, and development of target organ damage with the development of CRAB (hyperCalcemia, Renal insufficiency, Anemia, Bone lesions) symptoms, which include anemia, renal failure, bone disease, and hypercalcemia [1,2,12]. Unfortunately, despite the introduction of modern therapeutic strategies, including proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies, MM remains an incurable disease [1].

Existing staging systems like International Staging System (ISS) and Revised ISS (R-ISS) do not fully capture the biological heterogeneity of the disease, particularly in resource-limited settings where Durie–Salmon staging is still widely used [3,10].

Prognostic assessment in MM is traditionally relies on systems incorporating serum biomarkers and cytogenetic abnormalities. However, these systems do not

fully reflect the biological heterogeneity of the tumor clone, particularly at the level of tumor–microenvironment interactions [3]. Thus, in many regions of Kazakhstan, the Durie–Salmon staging system is still mainly used in everyday practice, which confirms the relevance of the study.

Flow cytometry is a cornerstone of MM diagnosis and monitoring, allowing detailed characterization of aberrant immunophenotypes [4,5,13]. Among these markers, CD56 (neural cell adhesion molecule) plays a key role in mediating plasma cell adhesion to the bone marrow niche. Its expression pattern varies across disease stages, being common in MM but reduced in MGUS and plasma cell leukemia, suggesting a role in disease biology and progression [6,12].

There is not much data on the value of CD56 expression level for the clinical course of MM [6,14]. Therefore, it is necessary to further evaluate the quantitative effect of CD56 expression on clinical outcomes in real conditions.

Relevance of the Study

Although molecular genetic testing has well-established prognostic significance in MM, access to cytogenetic and molecular techniques remains limited and is largely restricted to tertiary referral centers in Kazakhstan [8,10]. As a result, many patients are stratified and treated without comprehensive biological risk assessment.

In contrast, plasma cell immunophenotyping by multiparameter flow cytometry is a routine and widely available diagnostic method across all regions of the country [4,5,7]. This enables the use of immunophenotypic characteristics, including CD56 expression, as practical and reproducible prognostic markers in real-world clinical practice [13].

The relevance of this approach is further enhanced by the expanding therapeutic landscape in MM. Along with proteasome inhibitors, immunomodulatory drugs and monoclonal antibodies are now widely used in first-line therapy [1,8]. However, financial constraints do

not always allow the upfront use of intensive quadruplet regimens for all patients. Therefore, biologically driven patient stratification based on accessible markers is crucial to optimize treatment allocation and healthcare resources [8].

2. Materials and Methods

Our retrospective study was conducted on the basis of the LLP National Research Oncology Center. For example, this study included 26 patients with newly

diagnosed MM who received treatment between 2023 and 2025.

Table 1 - Clinical and Demographic Characteristics of Patients

Characteristics	CD56-негативные, n=4	CD56 ≤30%, n=10	CD56 >30%, n=12
Total patients, n (%)	4 (15)	10 (38)	12 (47)
Age, year, median (min–max)	55 (52–65)	57 (47–62)	55 (41–70)
Stage Durie–Salmon I, n (%)	0 (0)	3 (30)	1 (8)
Stage Durie–Salmon II, n (%)	1 (25)	6 (60)	5 (42)
Stage Durie–Salmon III, n (%)	3 (75)	1 (10)	6 (50)
Plasmacytoma, n (%)	2 (50)	1 (10)	3 (25)
Renal involvement, n (%)	0 (0)	1 (10)	1 (8)
Bone marrow plasma cells % median (min–max)	36 (11–68)	31,4 (11,8–80)	31 (11–53,8)

Plasma cell immunophenotyping was performed using multicolor flow cytometry with standardized EuroFlow antibody panels at the University Medical Center CF (Astana, Kazakhstan) [7,18].

Our study included only patients with more than 10% of clonal plasma cells, as lower levels of infiltration are associated with limited prognostic value [11,13,14]. This analysis included only cases with an aberrant plasma cell (PS) immunophenotype, which makes it

possible to distinguish between malignant and normal PS in accordance with international recommendations [4,7].

All patients were stratified into 3 groups: CD56-negative, CD56 ≤30%, and CD56 >30%. All patients received VCD induction therapy (bortezomib, cyclophosphamide, dexamethasone). Treatment response was assessed according to IMWG criteria [3,11]. OS was analyzed using the Kaplan–Meier method.

3. Results

Response to Induction Therapy

When assessing the response in these patient groups, it was found that CD56 negative and CD56>30%

had a lower response rate of up to 50%, while the CD56 <30% group had a 90% response rate.

Table 2 - Response after Induction Therapy

CD56 expression	n (%)	CR, n (%)	VGPR, n (%)	PR, n (%)	Refractory, n (%)
CD56-negative	4	0 (0)	2 (50)	0 (0)	2 (50)
CD56 ≤30%	10	1 (10)	0 (0)	8 (80)	1 (10)
CD56 >30%	12	0 (0)	2 (17)	4 (34)	6 (49)

Our results are comparable with previous reports indicating that both the absence of CD56 and the altered adhesive properties of plasma cells are associated with decreased sensitivity to standard induction regimens [6,9,14].

Overall Survival

Twenty-four-month OS rates were 73% in CD56-negative patients, 100% in patients with CD56 ≤30%, and 76% in patients with CD56 >30%. No deaths were recorded in the CD56 ≤30% group. Differences between groups did not reach statistical significance (p=0.31).

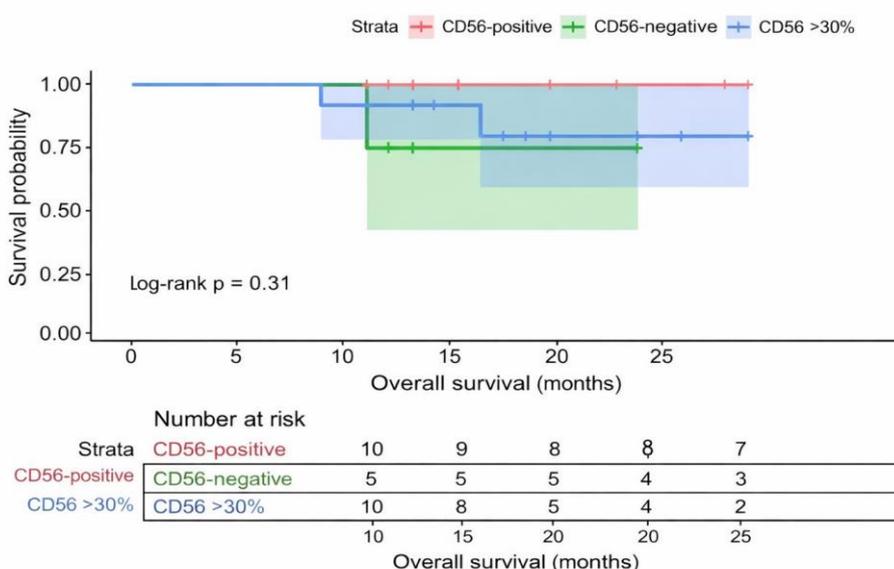


Figure 1 - Overall survival of patients according to the level of CD56 expression

4. Discussion

Our findings suggest a relationship between CD56 expression levels on plasma cells and clinical outcomes in newly diagnosed MM. We observed the most favorable outcomes in patients with moderate CD56 expression (≤30%), which may correspond to a less aggressive biological phenotype.

CD56 serves as a key adhesion molecule that facilitates interactions between plasma cells and various components of the bone marrow microenvironment, including stromal cells, extracellular matrix, and cytokine networks [6,9]. Its expression is typical in MM but notably reduced in MGUS, plasma cell leukemia, and extramedullary presentations, highlighting its relevance in tumor biology [6,12].

Prior studies indicate that loss of CD56 is associated with adverse features such as extramedullary spread, circulating plasma cells, plasmablastic morphology, and shorter overall survival [6,13-14]. Meta-analyses corroborate that CD56-negative MM carries a poorer prognosis compared to CD56-positive disease, though the effect size may vary across cohorts and treatments [8,14].

In our patient group, CD56-negative cases also showed a higher incidence of primary refractoriness, aligning with the concept that diminished CD56 expression may reduce microenvironmental dependence and lower sensitivity to proteasome inhibitor-based regimens [6,9].

Interestingly, we also noted that strong CD56 expression (>30%) correlated with less favorable outcomes relative to moderate expression. Although this phenomenon remains underexplored in the literature, emerging data propose that intense NCAM-mediated adhesion might activate pro-survival signaling and foster drug resistance [14-16].

The identification of a subgroup with moderate CD56 expression and optimal outcomes supports the concept of nonlinear relationships between immunophenotypic marker intensity and clinical behavior. Similar patterns have been described for other

plasma cell antigens, including CD38 and CD117, further supporting the biological plausibility of our findings [14-16].

International recommendations emphasize the role of standardized multiparameter flow cytometry not only in diagnosis but also in prognostic stratification and minimal residual disease assessment [7,17-19]. In resource-limited settings, quantitative assessment of CD56 expression may represent a valuable tool for personalized treatment planning at the time of diagnosis [4,8].

5. Conclusion

CD56 expression on plasma cells is a clinically relevant and accessible prognostic factor in patients with newly diagnosed multiple myeloma [6,13-15]. Incorporation of flow cytometry data into routine clinical decision-making may support personalized first-line treatment selection, optimize therapeutic strategies in real-world practice, and contribute to rational healthcare resource utilization [1,8,17].

Conflict of Interest. The authors declare no conflict of interest.

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Жаңадан диагноз қойылған көптік миеломасы бар науқастарда CD56 экспрессиясының плазмалық жасушаларға әсері

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Түйіндеме

Өзектілігі. Көптік миелома (KM) - өзгермелі клиникалық ағымы және терапияға реакциясы бар гетерогенді гематологиялық қатерлі ісік [1,2]. Өкінішке орай, көптік миелома әлі де емделмейтін ауру болып табылады және пациенттердегі жалпы өмір сүру деңгейінің (OS) және прогрессивті еркін өмір сүру деңгейінің (PFS) айырмашылығы тәуекел тобына байланысты өзгереді. Тәуекел топтарын стратификациялау үшін жоғары технологиялық молекулалық-генетикалық зерттеулерге қол жетімділіктің шектеулі болуына байланысты, әсіресе ағындық цитометрия деректері негізінде қол жетімді болжамды маркерлерді зерттеу өзекті болып қала береді [1,8].

Мақсаты. Біздің зерттеуімізде біздің мақсатымыз патологиялық плазмалық жасушалардағы CD56 экспрессиясының деңгейін және олардың индукциялық терапияға объективті жауап беру жиілігіне және жаңадан диагноз қойылған көптік миеломасы бар науқастардың жалпы өмір сүру деңгейіне әсерін бағалау болды.

Материалдар мен әдістер. Біз Қазақстанның Астана қаласындағы Ұлттық Онкологиялық Ғылыми-Зерттеу Орталығында емделіп жатқан жаңадан диагноз қойылған 26 көптік миеломасы бар науқасқа ретроспективті бір орталықты талдау жүргіздік. Плазмалық жасушаларды иммунофенотиптеу үшін біз Стандартталған EuroFlow хаттамасына сәйкес ұсынылған антиденелер панельдерімен түрлі-түсті ағындық цитометрияны қолдандық [7,17]. Халықаралық ұсыныстарға сәйкес [4,7,13] тек $\geq 10\%$ клондық плазмалық жасушалары және аберрантты иммунофенотипі бар емделушілер ғана енгізілді. Пациенттер CD56 экспрессия деңгейіне сәйкес стратификацияланды. Барлық науқастар VCD индукциялық терапиясын алды. Жауап IMWG критерийлері бойынша бағаланды және OS каплан–Мейер қисықтары арқылы талданды [3,11].

Нәтижелер. CD56 экспрессиясы $\leq 30\%$ пациенттерде объективті реакциялардың жоғары көрсеткіштері және 24 айдағы жалпы өмір сүрудің 100% байқалды, ал CD56 экспрессиясы теріс пациенттерде және CD56 экспрессиясы $>30\%$ пациенттерде бастапқы отқа төзімділік және жалпы өмір сүрудің төмендеу тенденциясы жоғары болды. Алайда, біздің зерттеуімізде айырмашылықтар статистикалық мәнге жете алмады ($p=0,31$), мүмкін пациенттердің шектеулі үлгісіне байланысты, бірақ біз нашар нәтижелерге қол жеткізу тенденциясын көріп отырмыз.

Қорытынды. CD56 экспрессиясы қол жетімді қосымша болжамдық маркер болып табылады және көптік миеломасы бар науқастарды емдеуді жекелендіру үшін пайдаланылуы мүмкін.

Түйін сөздер: көптік миелома, CD56, ағындық цитометрия, иммунофенотиптеу, болжам.

Влияние экспрессии CD56 на плазматических клетках у пациентов с впервые диагностированной множественной миеломой

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Резюме

Актуальность. Множественная миелома (ММ) - это гетерогенное гематологическое злокачественное новообразование с различным клиническим течением и ответом на терапию [1,2]. К сожалению, ММ по-прежнему остается неизлечимым заболеванием, и разница в показателях общей выживаемости (ОВ) и безрецидивной выживаемости (БРВ) у пациентов варьируется в зависимости от группы риска. В связи с ограниченным доступом к высокотехнологичным молекулярно-генетическим исследованиям для стратификации групп риска остается актуальным изучение более доступных прогностических маркеров, в частности, на основе данных проточной цитометрии [1,8].

Цель. Целью нашего исследования было оценить уровень экспрессии CD56 на патологических плазматических клетках и их влияние на частоту объективного ответа на индукционную терапию и ОВ у пациентов с впервые выявленной ММ.

Материалы и методы. Мы провели ретроспективный одноцентровый анализ у 26 впервые выявленных пациентов с ММ, проходивших лечение в Национальном научном онкологическом центре в Астане, Казахстан. Для иммунофенотипирования плазматических клеток мы использовали многоцветную проточную цитометрию в соответствии со стандартизированным протоколом EuroFlow с рекомендованными панелями антител [7,17]. В соответствии с международными рекомендациями [4,7,13] в исследование были включены только пациенты с более чем 10% клональных плазматических клеток и аберрантным иммунофенотипом. Пациенты были распределены по уровням экспрессии CD56. Все пациенты получали индукционную терапию VCD. Ответ на терапию оценивали в соответствии с критериями IMWG, а ОВ анализировали с использованием кривых Каплана-Майера [3,11].

Результаты. Высокие показатели объективного ответа и 100%-ная общая выживаемость в течение 24 месяцев наблюдались у пациентов с экспрессией CD56 $\leq 30\%$, в то время как у пациентов с отрицательной экспрессией CD56 и с экспрессией CD56 $>30\%$ чаще наблюдалась первичная рефрактерность и тенденция к снижению общей выживаемости. Однако в нашем исследовании различия не достигли статистической значимости ($p=0,31$), возможно, из-за ограниченной выборки пациентов, но мы видим тенденцию к ухудшению результатов.

Выводы. Экспрессия CD56 является доступным дополнительным прогностическим маркером и может быть использована для персонализации лечения пациентов с ММ.

Ключевые слова: множественная миелома, CD56, проточная цитометрия, иммунофенотипирование, прогноз.