Original Article

Comparison the Clinical Features of Newly Diagnosed Multiple Myeloma Patients According to CD23 Expression Status

Yeni Tanı Multipl Miyelom Hastalarının CD23 Ekspresyon Durumuna Göre Klinik Özelliklerinin Karşılaştırılması

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ABSTRACT

Introduction: The aim of the study was to evaluate the relationship between CD23 expression status and clinical features in multiple myeloma patients.
Materials and methods: We retrospectively analyzed the data of 196 patients diagnosed with multiple myeloma in our institution between May 2010 and August 2018.
Results: Compared to the CD23 negative group, in the CD23 positive group, the incidence of anemia was significantly lower, and the incidence of CD20 expression and the rate of R-ISS stage 1 patients was significantly higher. No similar association was found between R-ISS and other cell surface markers
Discussion: In conclusion, clinical presentations of multiple myeloma patients with aberrant CD23 expression show some clinical differences from those without. The fact that MM patients with CD23 expression were clustered in the favorable prognostic group according to R-ISS drew attention to its prognostic value. For MM patients, the addition of CD23 to the routine flow cytometry panel may be considered. In this respect, examination of CD23 expression is required in a larger group of cases to assess its prognostic value in MM.

Keywords: Multiple myeloma, Immunophenotyping, Flow cytometry, Cytogenetics, R-ISS

ÖZET

Giriş: Çalışmanın amacı, multipl miyelom hastalarında CD23 ekspresyon durumu ile hastaların klinik özellikleri arasındaki ilişkiyi değerlendirmektir.
Gereç ve yöntemler: Mayıs 2010 ile Ağustos 2018 tarihleri arasında kurumumuzda multipl miyelom tanısı alan 196 hastanın verilerini retrospektif olarak inceledik.
Bulgular: CD23 negatif gruba kıyasla CD23 pozitif gurupta anlamlı olarak anemi insidansı düşük, CD20 ekspresyon insidansı yüksek ve R-ISS evre 1 hasta oranı fazla gözlendi. R-ISS ile diğer hücre yüzey markırları arasında ise benzer bir ilişki bulunmadı.
Tartışma: Sonuç olarak, aberran CD23 ekspresyonu olan multipl miyelom hastalarının klinik prezentasyonları bazı klinik farklılıklar göstermektedir. CD23 ekspresyonu olan MM hastalarının önemli kısmının R-ISS'ye göre iyi prognostik grupta yer alması CD23'ün prognostik değerine dikkat çekmiştir. MM hastaları için rutin akım sitometri paneline CD23'ün eklenmesi düşünülebilir. Bu açıdan, CD23'ün MM'deki prognostik değerini araştırmak için daha geniş bir vaka grubunda CD23 ekspresyonunun incelenmesi gereklidir.

Anahtar kelimeler: Multipl miyelom, İmmünofenotipleme, Akış sitometrisi, Sitogenetik, R-ISS

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Introduction

Malignant plasma cells (PC) have abnormal antigen expressions that allow an analysis by flow cytometry to separate them from normal/reactive PC, so that can be used for diagnosing, monitoring residual disease and predicting the prognosis[1]. Multiple studies have demonstrated the prognostic value of antigen expression patterns by neoplastic PC[2–4]. Different results have been reported over the past years regarding the phenotype of clonal PC and clinical correlations, in MM. Nevertheless, prognostic value of immuno-phenotyping in MM remains questionable. And also, it is reported that the potential prognostic impact of the immunophenotypic characteristics might be related to the underlying cytogenetic abnormalities[2,5]

CD23 is a transmembrane low-affinity IgE Fc receptor found on the cell surface and has activities associated with cytokine modulation and B-cell growth factor function[6]. CD23 is well described in some hematological malignancies and is particularly helpful in the differentiation of chronic lymphocytic leukemia from mantle cell lymphoma by flow cytometry[7]. Also, CD23 expression has been reported in approximately 10% of multiple myeloma cases at diagnosis. However, there is a limited data in the literature evaluating the role of CD23 in multiple myeloma, and this hypothesis has not been proved whether or not affecting the clinical outcomes in newly diagnosed patients with MM [8–10]. Therefore, we have retrospectively evaluated the immuno-phenotypic profile of the PCs including CD23 expression in a series of 196 patients with newly diagnosed multiple myeloma.

Materials and Methods

Patient Selection and Basic Characteristics: Between May 2010 and August 2018, 196 patients diagnosed with symptomatic multiple myeloma in our institution were included in this cross-sectional study. All data were recorded from patients' chart files and/or electronic medical records. Our retrospective study was conducted in accordance with the Declaration of Helsinki and institutional ethics committee approval was obtained.

The diagnosis of myeloma was established in each patient according to the criteria recently defined by the International Myeloma Working Group[11] and was staged according to the criteria of International Staging System (ISS) and R-ISS[12]. We have recorded the full clinical information including patient age, gender, laboratory parameters such as serum ß2-microglobulin, albumin, calcium, hemoglobin, lactate dehydrogenase, serum creatinine concentrations, and immuno-globulin type of monoclonal protein, image study such as lytic bone lesions and plasmacytoma, surface antigen expression patterns analyzed by Multicolor Flow Cytometry (MFC), and cytogenetic abnormalities before any therapy. Fluorescence in situ hybridization (FISH) analyses were performed in patients for detection of t (4;14), t (14;16), t (11;14), del(13q14), del(17p13) and del(11q22.3). MFC analysis was performed in in the Clinical Flow Cytometry Laboratory of our institution using antibodies against CD38, CD138, CD19, CD20, CD45, CD117, CD56, BCL-2 and CD23. The expression levels of CD19, CD20, CD45, CD117, CD56, BCL-2 and CD23 in CD38 and CD138 positive cells were evaluated using a six-color panel of antibodies. At least 70 000 events were routinely acquired using a FACS Canto II flow cytometer with FACSDIVA software (BD Biosciences). All analyses also included an isotype-matched control tube containing APC-labeled CD38 to establish the positive staining threshold for plasma cells. A surface antigen expression in patients was defined as positive when 20% of the CD138+ population expressed this antigen above the cutoff.

Table 1. Clinical and laboratory characteristics of the 196 patients enrolled in the study at diagnosis

Patients Characteristics	
Median age, y (range)	63 (35-85)
Gender, n (%)	
▪ Male	115 (58.7)
▪ Female	81 (41.3)
Type of M component, n (%)	
▪ IgG	101 (51.6)
▪ IgA	49 (25)
▪ IgM	2 (1)
▪ IgD	1 (0.5)
▪ Biclonal	1 (0.5)
▪ Light chain only	41(20.9)
▪ Non-secretory	1 (0.5)
R-ISS, n (%)	
▪ I	34 (17.3)
▪ II	124 (63.3)
▪ III	38 (19.4)
Hemoglobin, g/dL (range)	9.7 (5.4-15.3)
β2-microglobulin, mcg/mL (range)	5.6 (1.4-120)
Creatinine, mg/dL (range)	1 (0.4-11.2)
Calcium, mg/dL (range)	9.4 (5.5-15.4)
Albumin, g/dL (range)	3.6 (1.3-5.1)
Lactate dehydrogenase, U/L (range)	194 (88-851)
Lytic lesion, n (%)	123 (62.8)
Plasmacytoma, n (%)	34 (17.3)
CD19(+), n (%)	57 (29.1)
CD20(+), n (%)	20 (10.2)
CD117(+), n (%)	57 (29.1)
CD56(+), n (%)	146 (74.5)
CD23(+), n (%)	23 (10.2)
CD45(+), n (%)	32 (16.3)
BCL-2(+), n (%)	60 (30.6)

BCL-2, B-cell lymphoma 2; CD, Cluster of Differentiation; Ig, Immunoglobulin; R-ISS,The Revised International Staging System.

Statistical Analysis

All statistical analyses were performed using SPSS (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.). Kolmogorov-Smirnov tests were used to test the normality of the data distribution. The data are expressed as median, minimum, maximum, the percentages and numbers. The Pearson chi-square test was used to compare the categorical variables. Mann-Whitney U test was used for comparison of continuous variables between the CD23 positive and CD23 negative groups. A two-sided p value <0.05 was considered to be statistically significant.

Results

Clinical and laboratory characteristics of the 196 patients at diagnosis are shown in Table 1. The patients consisted of 115 men and 81 women ages ranging from 35 to 85 years. According to the R-ISS, 17.3% of patients were stage I; 63.3%, stage II; and 19.4%, stage III. Of 196 PCMs, 23 (10.2%) were found to be CD23 positive by MFC at diagnosis. As shown in Table 2, age, sex, creatinine, albumin, lactate dehydrogenase, beta-2 microglobuline and calcium level, bone lesions, expression of surface antigens were similar for patients with CD23 positive and for those with CD23 negative. Compared with those of CD23 negative patients, in CD23 positive patients, the rate of patients with hemoglobin value <10 g/dl was less (30% vs 55.7%, P=0.029) and CD56 positive patient rate was greater (35% vs. 7.4%, P<0.001). There was no significant relationship between t (11;14) and the CD23 level (p>0.05). There were no statistically significant differences between R-ISS score and the CD45, CD56, CD117, CD19, CD20, BCL-2 levels (all p>0.05); whereas CD23 levels were more expressed in R-ISS 1 score patients compared to the R-ISS 2 and R-ISS 3 patients (p=0.017).

Table 2. Demographical and clinically comparisons of the CD23 (+) and CD23 (-) patients

	CD23 (+) n=20	CD23 (-) n=176	p
Age, (median, min, max)	60.5 (41-83)	64 (35-85)	0.369
Male/Female, n/n	12/8	73/103	0.899
Hb level <10, n (%)	6 (30)	98 (55.7)	0.029*
Beta-2 microglobulin ≥5.5, n (%)	6 (30)	94 (53.4)	0.047*
LDH >240 IU/L, n (%)	3 (15)	48 (27.3)	0.236
Albumin <3.5g/dL, n (%)	7 (35)	69 (39.2)	0.715
Creatinine ≥ 2 mg/dL, n (%)	2 (10)	42 (23.9)	0.159
Calcium ≥ 11 mg/dL, n (%)	2 (10)	21 (11.9)	0.799
Lytic lesions, n (%)	12 (60)	111 (63.1)	0.788
CD19 (+), n (%)	8 (40)	49 (27.8)	0.257
CD20 (+), n (%)	7 (35)	13 (7.4)	<0.001*
CD117 (+), n (%)	7 (35)	50 (28.4)	0.539
CD56 (+), n (%)	14 (70)	132 (75)	0.627
Bcl-2 (+), n (%)	7 (35)	53 (30.1)	0.653
CD45 (+), n (%)	3 (15)	29 (16.5)	0.865

BCL-2, B-cell lymphoma 2; CD, Cluster of Differentiation; Ig, Immunoglobulin; LDH, Laktat dehidrogenaz; R-ISS,The Revised International Staging System. *, p<0.05 regarded as statistically significant.

These results were also found similar using the ISS scores.

There were no statistically significant differences between FISH results [TP53 deletion at 17p13, t (4;14), t (14;16), 11q22 deletion, 13q14, and t (11;14)] and the CD45, CD56, CD117, CD19, CD20, BCL-2 and CD23 levels (all p>0.05).

Discussion

This is the first study evaluating and comparing the clinical outcomes of the newly diagnosed MM patients based on their CD23 expressions. The main finding of this study is: The clinical presentation of multiple myeloma patients with aberrant CD23 expression showed less anemia and more frequent CD20 expression compared to patients without CD23 expression, and there was also a correlation between CD23 expression and R-ISS.

The clinical course of multiple myeloma is various; new cytogenetic mutations may develop and available antigenic markers may be lost in the course of the disease, or the aberrant antigen expressions may be gained. For a disease with such heterogeneity and a dynamic change, predicting prognosis may be difficult. Although an effective prognostic classification is made with current prognostic tools such as ISS and R-ISS, there may be some patients with a different prognosis than expected despite this classification. Therefore, the relationship between immunophenotypic characteristics and prognosis from past to present has been the subject of many studies. An antigen expression at diagnosis may be associated with some clinical features or may provide a cross-sectional prognostic information. Although there are many studies on this subject, CD23 is not well described in

multiple myeloma compared to other hematological malignancies.

Previous studies investigating CD23 expression in MM patients focused on the correlation between CD23 and t (11,14). However, contrary to these studies, there was no correlation between CD23 expression and t (11,14) in our study.

Ruiz-Argüelles et al.[8] identified CD23 as an uncommon antigen and interrelated it with a possible poor prognosis. Although the number of cases was small, Walters et al.[9] reported the rate of CD23 expression in PCM as 10%. CD23 expression did not correlate with laboratory data, but all five CD23 positive cases displayed abnormalities of chromosome 11. Based upon this report, the relationship between t (11;14) positivity and CD23 expression has been investigated by Buonaccorsi et al.[10] They performed a retrospective study on 42 bone marrow biopsies from patients with PCM who had a documented t (11;14) (q13; q32) by conventional cytogenetic analysis or FISH. Of 42 PCMs, 19 (45.2%) were found to be CD23(+) by IHC. They reported that, unlike our results, there was no difference in clinical stage between CD23(+) and CD23(-) patients. This can be explained by the different design of their study in which CD23 related analyzes were performed only in patients with t (11,14) positive. As is known, t (11,14) is defined as standard risk within the cytogenetic risk classification of MM. Therefore, these CD23 related results obtained from (11,14) positive patients cannot be generalized to all MM patients.

Conclusion

The presence of a plasma cell immunophenotype correlating with R-ISS, an accepted tool for prognostic classification of multiple myeloma, may indirectly suggest a prognostic value. As a result, it suggests the idea that CD23 can be integrated into the flow cytometric immunophenotyping panel for multiple myeloma. Due to the correlation observed in our cohort between CD23 and R-ISS, additional examination of a larger set of cases is necessary in order to assess the prognostic relevance of CD23 expression in MM.

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