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Absence of both CD56 and CD117 expression on malignant plasma cells is related with a poor prognosis in patients with newly diagnosed multiple myeloma

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ABSTRACT

We retrospectively evaluated the association between the expression of CD56 and CD117 on neoplastic plasma cells and patients prognosis in 50 newly diagnosed multiple myeloma (MM) patients. The overall survival (OS) was measured and Cox proportional hazards model was used to evaluate CD56 and CD117 as possible prognostic factors for OS. CD56+ and CD117+ were detected in 74% and 32% multiple myeloma cases, respectively. In Kaplan–Meier analysis, CD56 and CD117 expression demonstrated potential prognostic impacts and were associated with longer OS (CD56: $p = 0.004$, CD117: $p = 0.022$), absence of both of them showed significantly shorter OS ($p = 0.046$ compared to CD56+/CD117+ group, $p = 0.014$ compared to CD56−/CD117+ or CD56+/CD117− group). Multivariate analysis showed that CD56 was independently prognostic of longer OS ($p = 0.012$). After induction chemotherapy, overall response rates (ORR) was higher in CD56-positive group compared to CD56-negative group (70.6% versus 30.0%, $p = 0.024$), however, there was no difference between CD117-positive and CD117-negative group (69.2% versus 58.1%, $p = 0.448$). This study demonstrated the prognostic value of CD56 and CD117 in patients with newly diagnosed MM patients. Absence of both of them was associated with the poorest prognosis.

1. Introduction

Multiple myeloma (MM) is the hematologic malignancy in which malignant plasma cells accumulate in bone marrow, causing extensive amounts of monoclonal protein (M-protein) and organ injuries resulting in anemia, hypercalcemia, bone lesions, and renal insufficiency. Malignant plasma cells express highly unique abnormal antigens, so they can be distinguished by Flow cytometry (FCM) for diagnosing, monitoring residual disease (MRD) during the process of treatment and even predicting the prognosis [1].

CD56 is an adhesion molecular and also believed a marker involved in anchoring plasma cells to stromal structures. Deficiency of CD56 has been associated with malignancy in plasma cells and down-regulation of it showed highly proliferation and spreading of malignant plasma cells [2–3]. CD117 is a tyrosine kinase receptor, which does not express onnormal plasma cells. Many studies have showed the expression of antigens such as CD56 and CD117 on malignant plasma cells are associated with the prognosis of MM [2–5], however, it does not reach consensus. In this study, we analyzed the expression status of CD56 and CD117 on myeloma cells from 50 newly diagnosed patients and their clinical relevance for evaluating the clinical significance.

2. Materials and methods

2.1. Ethics statement

This study was approved by the Institutional Review Board (IRB) Institutional of the Second Hospital of Anhui Medical University. Study was performed in accord with the principles of the Declaration of Helsinki. All patients agreed to use their medical records for research.

2.2. Patients

Bone marrow specimens from 50 newly diagnosed MM patients, who had the full clinical information including laboratory

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parameters (serum β2-microglobulin, albumin, calcium, hemoglobin, lactate dehydrogenase, serum creatinine concentrations, and immunoglobulin type of monoclonal protein) before any therapy, were examined at the second hospital of Anhui medical university from November 2009 to February 2015. Concurrence of autoimmune disease, human immunodeficiency virus (HIV) and syphilis was excluded for all enrolled individuals. All patients were given thalidomide 150–250 mg per day for basic treatment. Risk group and disease progression were defined according to the International Myeloma Working Group (IMWG) risk stratification and response criteria for MM, respectively [6–7].

2.3. Flow cytometry

Bone marrow aspirate specimens were tested on a 2-laser FC-500 (Beckman Coulter, Miami, FL, USA). Whole BM samples were stained using the following three-color combinations of antibodies (FITC/PE/PeCy5), such as, CD34/CD71/CD45, CD38/CD138/CD45, CD19/CD56/CD45, CD33/CD117/CD45, CD64/CD13/CD45, CD22/CD20/CD45, CD23/CD10/CD45, and cyto-Kappa/cyto-Lambda/CD45 (Beckman Coulter, Miami, FL, USA). All samples were anticoagulated with heparin and examined within 4 h. About 100 μl of anti-coagulated bone marrow sample was labeled with pre-conjugated monoclonal antibodies at 25 °C for 20 min in the dark. After incubation, red blood cells were lysed and washed in PBS three times. Stained cells were quickly detected and analyzed using the FC-500 (Table 1).

2.4. Statistical analysis

Statistical analysis was carried out using SPSS 16.0 software. The correlation between the CD56/CD117 and clinical parameters was assessed by the chi-square test or Fisher's exact test. Overall survival (OS) was calculated from the date of diagnosis to death from any cause and estimated using the Kaplan–Meier method and two-tailed log-rank test. The Cox proportional hazards model was used to evaluate CD56 and CD117 as prognostic factors for OS and to adjust for other known prognostic factors. All two-sided p-values < 0.05 were determined to be statistically significant.

3. Results

3.1. Patient characteristics and antigen expression

A total of 50 newly diagnosed patients with MM were eligible for this analysis. The median age was 63 (41–79) years old, and 29 (58%) were male, 21 (42%) were female. The expression of CD38 and CD138 were detected in 100% of cases, the expression of CD56 accounts for 74% (37 of 50) and CD117 accounts for 32% (16 of 50) in all neoplastic plasma cells. CD33, CD20 and CD19 expression were relatively uncommon compared with CD56, CD117, CD38 and CD138 (Fig. 1).

The distribution of baseline characteristics for 50 newly diagnosed MM patients based on positive or negative of CD56 and CD117 is presented in Table 2. CD117 negativity showed strong association with serum creatinine concentrations ($p = 0.007$). However, it did not showed any association with other baseline clinical characteristics (age, sex, serum β2-microglobulin, albumin, cal-

Table 1
Clinical characteristics of newly diagnosed multiple myeloma patients.

Characteristics	CD56 number		p	CD117 number		p
	Positive ($n = 37$)	Negative ($n = 13$)		Positive ($n = 16$)	Negative ($n = 34$)	
Age(≥60 years)	24	9	1.000	10	23	0.720
Sex, male	18	10	0.077	10	18	0.525
ISS stage III	20	8	0.640	7	21	0.231
Bone destruction	27	7	0.473	9	25	0.222
Hemoglobin(<100 g/L)	32	9	0.214	13	28	1.000
Creatinine(>176.8 umol/L)	11	5	0.731	1	15	0.007
Calcium(>2.75 mmol/L)	7	2	1.000	1	8	0.240
Albumin(<30 g/L)	23	9	0.746	9	23	0.434
β2-MG (>5.5 mg/dL)	20	8	0.640	7	21	0.231
Monoclonal heavy chain			0.516			0.531
IgG	21	7		7	21	
IgA	11	3		6	8	
IgD	0	1		0	1	
Light chain only	5	2		3	4	
BM plasma cell ≥30%	24	9	1.000	12	21	0.357
Front-line treatment			0.427			0.104
Bortezomib-based	12	3		7	8	
VAD-based	22	7		6	23	
others	3	3		3	3	

Characteristics	Number(%) or median(range)
Age	63(41–79)
Sex, male/female	29:21
WBC, $\times 10^9$/L	4.62(0.7–15.6)
Hemoglobin, g/dL	68.5(41–133)
Platelet, $\times 10^9$/L	122(14–295)
LDH, U/L	136(68–512)
Creatinine, umol/L	116(46–806)
Calcium, mmol/L	2.2(1.5–4.1)
Albumin, g/dL	26.3(14.8–44.1)
β2-MG, mg/dL	5.94(0.85–66.6)
ISS stage, I:II:III	3:19:28
IgG:IgA:IgD:IgM:IgE:light chain type	28:14:1:0:0:7
BM aspirate plasma cell,%	37.75(2.5–75)