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Original Article

Correlation between CD45, CD31 and prognosis in patients with multiple myeloma

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Abstract: Objective: To explore the correlation between the expressions of CD45 as well as CD31 and the prognosis in patients with multiple myeloma. Methods: A prospective cohort study was designed, and 120 patients with multiple myeloma were selected as subjects, among them, 30 patients with CD45 (+) and CD31 (-) were included in CD45 (+) group; 30 with CD31 (+) CD45 (-) were in CD31 (+) group; 30 with CD45 (+) and CD31 (+) were in CD45 (+) CD31 (+) group; 30 with CD31 (-) and CD45 (-) were in CD31 (-) CD45 (-) group. All patients received treatment of bortezomib and long-term follow-up. The objective remission rate (ORR), progression-free survival (PFS) and overall survival (OS) of all patients were observed, and the relationship between the expressions of CD45/CD31 and the prognosis was analyzed in patients after treatment of bortezomib. Results: Analysis of variance showed that there were significant differences in platelets (Plt), lactate dehydrogenase (LDH), beta-2 microglobulin (β_2MG), and plasma cell infiltration in bone marrow among the four groups (all P<0.05). SNK-q test showed that the Plt of patients was significantly higher and the β_2MG, LDH and plasma cell infiltration in bone marrow were significantly lower in CD45 (+) group, CD31 (+) group and CD45 (+) CD31 (+) group than in CD45 (-) CD31 (-) group (all P<0.05). The distributions of patients with complete response, partial response, stable disease and progressive disease in the four groups were significantly different (P<0.05). The ORR was significant lower in CD45 (-) CD31 (-) group (33.33%) than that in CD45 (+) group (66.33%), CD31 (+) group (60.00%), and CD45 (+) CD31 (+) group (66.67%) (P<0.05), while there was no significant difference between the CD45 (+) group, CD31 (+) group and CD45 (+) CD31 (+) group (P>0.05). The differences in the PFS and OS were significant among the four groups after treatment (both P<0.001). Kaplan-Meier survival analysis suggested that the PFS and OS in the CD45 (-) CD31 (-) group were significantly shorter than those in the CD45 (+) group, CD31 (+) group and CD45 (+) CD31 (+) group after treatment (all P<0.01). Log-rank test showed that there was no significant difference in PFS and OS between CD45 (+) group, CD31 (+) group and CD45 (+) CD31 (+) group (all P>0.05). Cox multiple regression model showed that the factors affecting the prognosis of patients were high LDH, CD45 (-), CD31 (-), and CD45 (-) plus CD31 (-). Conclusion: CD45 (-) and CD31 (-) are related to the poor prognosis in patients with multiple myeloma, and the prognosis between patients with CD45 (+), CD31 (+) or with both CD45 (+) CD31 (+) was not significantly different.

Keywords: Multiple myeloma, antigen, CD45, CD31, prognosis

Introduction

Multiple myeloma as a malignant proliferative disease of the blood system originates from the B cell line, produces monoclonal immunoglobulin and leads to damage on organs and tissues [1]. Multiple myeloma accounts for 12% to 15% of hematological malignancies, 1.4% of all malignant tumors, and 1.9% of all cancer deaths [2]. According to the cancer epidemiological statistics released by GLOBOCAN in 2012, the incidence of multiple myeloma was 0.8/100,000 in China, 3.2/100,000 in Europe and 4.3/100,000 in the United States [3]. Epidemiological data showed an annual increase in the incidence of multiple myeloma worldwide [4, 5]. At present, the pathogenesis of multiple myeloma is not yet clear, and researches on the pathogenetic factors are controversial [6, 7].

The clinical manifestations of patients with multiple myeloma are diverse, and the prognosis of patients is heterogeneous. Currently, del

(17p), t(14;16) and t(14;20) are commonly agreed as factors for poor prognosis [7]. Nevertheless, more factors that are easy to detect and stable in clinical testing are urgently needed for the evaluation of prognosis. The different antigens in B cell surface are the main reason for the potential varied proliferation and differentiation of multiple myeloma cells [8, 9]. Immune markers that effectively reflect the biological behavior of multiple myeloma cells are beneficial to the prediction of prognosis and the adjustment of treatment regimens. CD45, as a single-chain transmembrane protein, exists on the surface of hematopoietic cells and belongs to the protein tyrosine phosphatase family [10]. Studies have shown that the survival time of patients with CD45 (-) is significantly shorter than that of patients with CD45 (+) [11-13]. However, previous studies have only focused on the expression of a single antigen, instead of the effect of multiple antigens on the prognosis of multiple myeloma. CD31, also known as platelet endothelial cell adhesion molecule, is stable on the surface of normal plasma cells [14]. CD31 has been proved to be associated with tumor angiogenesis. Kumar et al. showed that CD31 can affect intramedullary angiogenesis in multiple myeloma cells by affecting the levels of epidermal growth factors [15]. However, there are few studies on the correlation between CD31 and the prognosis of multiple myeloma.

Therefore, this prospective cohort study innovatively analyzed the correlation between CD45/CD31 and the prognosis of multiple myeloma, so as to provide reference for the evaluation of the clinical prognosis of multiple myeloma.

Materials and methods

Baseline data

A prospective cohort study was designed. A total of 120 patients diagnosed with multiple myeloma and treated in Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University from January 2012 to January 2020 were included as study subjects. Patients were informed about the study protocol and signed written informed consent voluntarily. This study was approved by the Ethics Committee of Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University.

Patients were eligible if they were diagnosed with multiple myeloma according to the criteria issued by the International Myeloma Working Group in 2009 [16], accepted the chemotherapy regimen BAD (bortezomib + Adriamycin + dexamethasone) or BCD (bortezomib + cyclophosphamide + dexamethasone), and did not receive an autologous stem cell transplantation.

Patients were excluded if they had other serious immune system diseases or other systemic malignancies, did not receive the prescribed chemotherapy regimens, had plasma cell leukemia, or failed to complete follow-up; had mental illness, failed to sign informed consent, or did not complete the study.

Methods

Among the 120 subjects, 30 patients with CD45 (+) and CD31 (-) were included in CD45 (+) group; 30 with CD31 (+) CD45 (-) were in CD31 (+) group; 30 with CD45 (+) and CD31 (+) were in CD45 (+) CD31 (+) group; 30 with CD31 (-) and CD45 (-) were in CD31 (-) CD45 (-) group. The demographic data of patients were recorded after admission, including gender, age, etc. Besides, we detected the clinical data of patients, including white blood cells (WBC), hemoglobin (Hb), platelet count (Plt), serum C-reactive protein (CRP), serum lactate dehydrogenase (LDH), serum β2-microglobulin (β_2MG), serum creatinine (Cre) and blood calcium (Ca). International Staging System (ISS) for multiple myeloma was used for staging [17]. Flow cytometry was used to detect the cellular immunophenotype: 2 mL of bone marrow fluid was collected by conventional bone marrow paracentesis and anticoagulated with EDTA [18]. Thereafter, CD 38-FITC, CD 45-APC, CD 56-PE, CD 19-Per CP-cy 5.5, CD 20-PE-cy 7, CD 54-PE, CD 138-Per CP-cy 5.5 and isotype control CD 31-PE were respectively added in proportion for 20-min incubation in dark. Then, the samples were added with 1.0 mL ???, incubated in dark for 10 min, washed, discarded for the supernatant and suspended with 500 pL of PBS. CD31 was purchased from Thermo Fisher Scientific, China (clone number: WM59), and the other antibodies were all purchased from BD, USA. A total of 7×10^4 cells were obtained using flow cytometry (FACS Canto, BD, USA) and BD FACS Diva software. The expression standard of CD45 was cMFIPC = MFIPC × 100/MFILYM.

Other antigens were seen positive when the expression was >20% [19]. All patients received a combined treatment including bortezomib (Ben Venue Laboratories Inc., J20050042, USA), and did not receive autologous hematopoietic stem cell transplantation. BAD or BCD regimen was given according to the physical condition of patients. After 4-8 weeks of chemotherapy, bortezomib only was given as maintenance treatment. A personal file was created for each patient for long-term follow-up, and all clinical data of patients were recorded in electronic summary tables.

Outcome measures

First, the correlation between the immunophenotype and clinical characteristics was analyzed. The immunophenotype was detected with flow cytometry, and patients with CD45 (+), CD31 (+), CD45 (+) CD31 (+), and CD45 (-) CD31 (-) were included in different groups for further comparison.

Second, the objective remission rate (ORR) of patients with different immunophenotypes [20] was analyzed. The efficacy of chemotherapy was graded according to the evaluation criteria of myeloma chemotherapy. Complete remission (CR) referred to negative immunofixation electrophoresis of serum and urine, negative M protein, and bone marrow plasma cells <5%; partial remission (PR) referred to ≥50% reduction of serum M protein, ≥90% decrease or <200 mg/24 h of 24 h urine M protein; stable disease (SD) referred to insignificant decrease or increase in serum M protein; disease progression (PD) was defined when M protein increased ≥10 g/L from the baseline ≥50 g/L, and the difference value of affected and non-affected sFLC increased by 25% or an absolute value of 100 mg/L. ORR = (CR + PR)/(CR + PR + SD + PD) × 100%.

Third, the survival of patients with different immunophenotypes [21] was analyzed. Progression-free survival (PFS) referred to the time from diagnosis to disease progression/death. The overall survival (OS) referred to the time from diagnosis to last follow-up or death. Kaplan-Meier survival curves were used for the survival curve plotting in the 4 groups of patients, and log-rank test was used to compare the differences in survival data between the groups.

Lastly, the factors affecting prognosis [22] were analyzed. Cox regression analysis model was used to analyze the factors affecting the prognosis.

Statistical analyses

SPSS24.0 was used for statistical analyses. The counted data were expressed as case/percentage (n, %), testes by χ^2 test (test level: two-tailed α=0.05). The measurement data were expressed as mean ± standard deviation and compared among 4 groups using analysis of variance (F test). When the results of F test were statistically different, SNK-q test was used to compare the differences between two groups. The distribution of ranked data was compared using Mann-Whitney U test. The differences in PFS and OS among the four groups were analyzed using Kaplan Meier survival curve and tested for differences between groups using log-rank. Cox regression analysis model was used to analyze the factors affecting the prognosis. P<0.05 was considered statistically significant.

Results

Baseline data

There was no significant difference in age, gender, ISS stage, and immunophenotypes among the four groups (all P>0.05). The levels of serum WBC, Hb, CRP, Cre and Ca among the four groups were not significantly different (all P> 0.05). Analysis of variance showed that there were significant differences in Plt, LDH, β_2MG and plasma cell infiltration in bone marrow among the four groups (all P<0.05). Further SNK-q test suggested that the Plt was significantly higher, and the LDH, β_2MG and plasma cell infiltration were significantly lower in the CD45 (+) group, CD31 (+) group and CD45 (+) CD31 (+) group than in CD45 (-) CD31 (-) group (all P<0.05). There was no significant difference in Plt, LDH, β_2MG and plasma cell infiltration in bone marrow among the CD45 (+) group, CD31 (+) group and CD45 (+) CD31 (+) group (P=0.134). See **Table 1**.

Comparison of ORR

All patients completed 4 courses of chemotherapy, and the efficacy of chemotherapy was evaluated. The distribution of cases of CR, PR,

Table 1. Sociodemographic and clinical data

Item	CD45 (+) group (n=30)	CD31 (+) group (n=30)	CD45 (+) CD31 (+) group (n=30)	CD45 (-) CD31 (-) group (n=30)	F/χ^2	P
Age (year)	56.5±8.3	57.4±9.0	58.1±8.6	57.7±9.5	0.772	0.641
Gender (male/female)	20/10	18/12	19/11	16/14	0.523	0.436
WBC (× 10^9/L)	3.91±0.90	4.11±1.03	3.82±0.71	4.01±1.12	0.819	0.116
Hb (mg/dL)	107.7±27.3	109.8±29.6	110.2±29.4	112.5±27.7	0.741	0.220
Plt (× 10^9/L)	75.8±19.7*	78.2±18.9*	76.3±18.7*	68.8±17.1	1.477	0.038
CRP (mg/dL)	0.27±0.23	0.30±0.26	0.32±0.25	0.25±0.20	0.866	0.097
LDH (IU/L)	240.5±52.3*	239±49.9*	251.2±45.7*	293.8±55.2	2.579	0.013
β_2MG (g/dL)	2.17±0.40*	2.20±0.53*	2.12±0.39*	5.46±0.83	9.527	0.001
Cre (mg/dL)	2.03±0.84	2.12±0.95	2.10±0.85	2.20±0.90	0.559	0.482
Ca (mg/dL)	10.5±2.3	11.1±2.9	10.7±2.5	11.2±3.0	0.928	0.101
Plasma cell infiltration in bone marrow (%)	10.2±5.8*	10.5±7.2*	9.3±6.5*	14.3±6.8	10.588	0.001
ISS stage (n)					0.221	0.754
Stage I	8	7	10	11		
Stage II	10	9	10	8		
Stage III	12	14	10	11		
Immunophenotype (n)					0.465	0.772
IgG	12	13	10	11		
IgA	5	4	6	6		
IgD	3	2	3	2		
IgM	2	2	1	1		
BJP	8	9	10	10		
Chemotherapy regimen (n)					0.239	0.798
BAD	18	14	17	15		
BCD	12	16	13	15		

Note: WBC: white blood cells; Hb: hemoglobin; Plt: platelets; CRP: C-reactive protein; LDH: lactate dehydrogenase; β_2MG: beta-2 micro-globulin; Cre: creatinine; Ca, calcium; ISS: international staging system; BJP: bence-jones protein. Compared with CD45 (-) CD31 (-) group, *P<0.05.

Table 2. Therapeutic effect of patients with different immunophenotypes

Efficacy	CD45 (+) group (n=30)	CD31 (+) group (n=30)	CD45 (+) CD31 (+) group (n=30)	CD45 (-) CD31 (-) group (n=30)	U/χ^2	P
CR	8	6	9	2	5.352	0.011
PR	11	12	11	8		
SD	6	7	9	13		
PD	5	5	1	7		
ORR	19 (63.33%)*	18 (60.00%)*	20 (66.67%)*	10 (33.33%)	5.221	0.001

Note: Compared with CD45 (-) CD31 (-) group, *P<0.05. CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: objective remission rate.

SD and PD in the 4 groups was statistically significant (P<0.05). The ORR was significantly lower in CD45 (-) CD31 (-) group (33.33%) than that in CD45 (+) group (66.33%), CD31 (+) group (60.00%) and CD45 (+) CD31 (+) group (66.67%) (P<0.05), while there was no significant difference between the CD45 (+) group, CD31 (+) group and CD45 (+) CD31 (+) group (χ^2=0.527, P=0.325). See **Table 2**.

Comparison of survival after treatment

The deadline of follow-up was January 31, 2020. The median follow-up time was 35 (8-80) months. A total of 26 patients were lost to follow-up. There were 5, 5, 7, and 9 cases lost to follow-up in CD45 (+) group, CD31 (+) group, CD45 (+) CD31 (+) group and CD45 (-) CD31 (-) group, respectively. The differences in PFS and OS among the four groups of patients were significant (both P<0.001). The PFS and OS of the CD45 (-) CD31 (-) group were significantly shorter than those of the CD45 (+) group, CD31 (+) group and CD45 (+) CD31 (+) group (all P< 0.01). Results of Log-rank test showed no significant difference among CD45 (+) group, CD31 (+) group and CD45 (+) CD31 (+) group

Table 3. Comparison of PFS in patients with different immunophenotypes

PFS (month)	CD45 (+) group (n=25)	CD31 (+) group (n=25)	CD45 (+) CD31 (+) group (n=23)	CD45 (-) CD31 (-) group (n=21)	U	P
Minimum PFS	16.2	15.4	16.5	9.3	12.585	<0.001
Maximum PFS	69.3	68.2	69.4	62.2		
Medium PFS	39.3	38.7	40.1	28.3		

Note: PFS: progression-free survival.

Table 4. Comparison of OS in patients with different immunophenotypes

OS (month)	CD45 (+) group (n=25)	CD31 (+) group (n=25)	CD45 (+) CD31 (+) group (n=23)	CD45 (-) CD31 (-) group (n=21)	U	P
Minimum OS	17.5	17.9	18.5	11.6	15.772	<0.001
Maximum OS	78.0	75.3	78.7	60.4		
Medium OS	43.0	42.8	44.5	32.0		

Note: OS: overall survival.

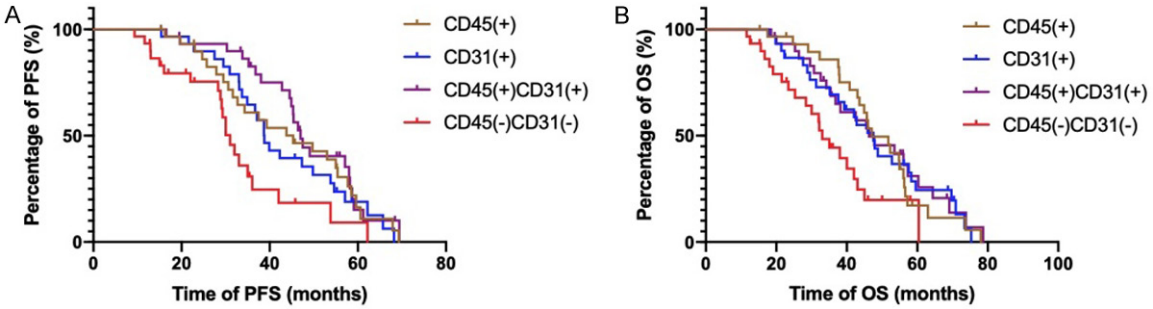

Figure 1. Survival of patients with different immunophenotypes. A: Comparison of PFS among 4 groups of patients; B: Comparison of OS among four groups of patients. PFS: progression-free survival; OS: overall survival.

(PFS: χ^2=0.638, P=0.226; OS: χ^2=0.356, P=0.552). See **Tables 3**, **4** and **Figure 1**.

Prognosis after chemotherapy

The survival time and clinical data of 94 patients were analyzed, and it was considered that Plt, LDH, β_2MG, and plasma cell infiltration in bone marrow may affect the prognosis. The Plt, LDH, β_2MG, and plasma cell infiltration in bone marrow were seen as binary variables [23]. Cox univariate regression analysis showed that Plt ≥150,000 (χ^2=0.982, P=0.047), LDH ≥211 (χ^2=1.025, P=0.031), β_2MG <3.5 (χ^2=0.955, P=0.048), plasma cell infiltration in bone marrow <30% (χ^2=1.012, P=0.042), CD45 (-) (χ^2=8.772, P=0.001), CD31 (-) (χ^2=8.983, P=0.011), and CD45 (-) CD31 (-) (χ^2=9.257, P=0.007) were related to poor prognosis in patients.

Cox multivariate regression analysis of above variables showed that LDH ≥211 (HR=2.44, 95% CI: 1.30-6.11, P=0.012), CD45 (-) (HR=2.82, 95% CI: 1.33-4.39, P<0.001), CD31 (-) (HR=2.85, 95% CI: 1.15-5.21, P<0.001), and CD45 (-) CD31 (-) (HR=2.90, 95% CI: 1.28-4.98, P<0.001) were risk factors for the poor prognosis. See **Table 5**.

Discussion

The immunophenotype of tumor cells can provide additional prognostic information as useful supplement for the prediction of prognosis [24]. This cohort study included patients with 4 different immunophenotypes, and analyzed the differences in treatment effect, survival data and the factors affecting prognosis in patients with multiple myeloma.

In terms of treatment efficacy, patients with CD45 (-) CD31 (-) showed a significant disadvantage, with the lowest ORR. The ORR of patients with CD45 (-) was significantly lower than that of patients with CD45 (+), which is

Table 5. Prognosis after chemotherapy by Cox multivariate regression analysis

Factors	HR	95% CI	P
Plt ≥150 000	1.01	0.25-2.48	0.103
LDH ≥211	2.44	1.30-6.11	0.012
β_2MG <3.5	1.13	0.23-1.98	0.207
Plasma cell infiltration in bone marrow <30%	1.08	0.29-2.51	0.099
CD45 (-)	2.82	1.33-4.39	<0.001
CD31 (-)	2.85	1.15-5.21	<0.001
CD45 (-) CD31 (-)	2.90	1.28-4.98	<0.001

Note: Plt: platelets; LDH: lactate dehydrogenase; β_2MG: beta-2 microglobulin; HR: hazard ratio; CI: confidence interval.

consistent with previous studies and is in line with our expectations [11-13]. In terms of survival, the results of this study showed that patients in the CD45 (-) CD31 (-) group had poor prognosis. The PFS and OS in the CD45 (-) CD31 (-) group were significantly shorter than those in the CD45 (+) group, CD31 (+) group and CD45 (+) CD31 (+) group. Moreau et al. believed that CD45 (-) myeloma cells had greater ability to transfer and clone and were less sensitive to apoptosis, so they can result in a poor prognosis [25]. Iriyama et al. studied the effect of immunophenotype on the prognosis of patients with multiple myeloma treated with bortezomib combined with dexamethasone and showed that CD45 (+) was an unfavorable factor for the prognosis of patients treated with bortezomib, which is inconsistent with the results of this study [26]. Oka et al. believed that the expression of CD45 in tumor plasma cells of patients with multiple myeloma was related to the prognosis of the patients, and it was necessary to find a treatment for patients with CD45 (-) so as to improve their poor prognosis [23]. The deviation here may be caused by the improvement of flow cytometry and the differences in ways of design, treatment regimens or the grouping methods [27, 28]. Even though there are lots of clinical regimens for the treatment of multiple myeloma, it is still necessary to screen the surface antigens that are relate to the prognosis of multiple myeloma.

The immunophenotype of normal plasma cells in the body is believed to be CD138 (+) CD54 (+) CD20 (+) CD19 (+) CD56 (+), while the immunophenotype of multiple myeloma cells is CD138 (+) CD54 (+) CD20 (+) CD19 (-) CD56 (+/-) CD20 (+/-) [29]. CD31 as complement of CD38 plays an important role in the pathogenesis of tumors. Researches on the mechanism of CD31 in tumor angiogenesis suggested that CD31 promoted the formation of blood vessels by activating matrix metalloproteinases and degrading extracellular matrix and vascular basement membrane [30, 31]. Nevertheless, there is no research on CD31 in angiogenesis in patients with multiple myeloma. Ouyang et al. confirmed that the expression of CD31 in patients with multiple myeloma was significantly related to CD54 [32]. This study innovatively studied the effect of CD31 expression on the prognosis of patients with multiple myeloma. The results showed that both CD31 (-) and CD54 (-) were risk factors for poor prognosis. Patients with CD31 (-) showed lower ORR, and shorter PFS and OS than patients with CD31 (+), which may be due to the negative correlation between CD31 and primitive plasma cells [32].

This study set up 4 groups: CD45 (+) group, CD31 (+) group, CD45 (+) CD31 (+) group and CD45 (-) CD31 (-) group to verify the impact of CD45 and CD31 on poor prognosis in patients with multiple myeloma, and to investigate whether the CD45 and CD31 can simultaneously affect the prognosis. It is worth noting that our data showed that negative expression of either CD45 or CD31 did not change the prognosis significantly. Only when both CD45 and CD31 were negatively expressed, the ORR, PFS and OS of patients were significantly different from patient with CD45 (+), CD31 (+), or CD45 (+) CD31 (+). This result is reported for the first time: one negative expression (either CD45 or CD31) will not result in a poor prognosis. The reason might be that CD45 and CD31 share the same pathway when affecting the disease progression of patients with multiple myeloma, thereby showing a correlation [15, 32].

There are still some limitations in this study. First, though chemotherapy was the choice of most patients and there were limited patients received bone marrow transplantation, this single-center cohort study had relatively small number of patients in each group, which may

result in certain bias. Second, our study showed a high rate of loss of follow-up due to the long follow-up time, which led to a further reduction of the sample size. Third, patients with multiple myeloma were almost incurable by chemotherapy, but the relapsed data after treatment were not analyzed in this study, which may also lead to certain bias. Lastly, the study of the correlation between CD31 and the prognosis of multiple myeloma was limited, so further research on the mechanism of CD31 expression in patients with multiple myeloma is still needed.

In summary, CD45 (-) and CD31 (-) are related to the poor prognosis of patients with multiple myeloma. Therefore, a set of targeted treatment plans should be constructed for these patients. In clinical treatment, the evaluation of efficacy should be highly valued, especially in patients with negative immunophenotypes of both CD45 and CD31.

Disclosure of conflict of interest

None.

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References

[1] Fan F, Malvestiti S and Shen Y. Multiple myeloma pathogenesis: the role of Junb in bone marrow angiogenesis. Blood 2019.

[2] Siegel RL, Miller KD and Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015; 65: 5-29.

[3] International Agency for Research on Cancer. Globocan 2012: estimated cancer incidence, mortality and prevalence worldwide in 2012. Globocan 2012.

[4] Velez R, Turesson I, Landgren O, Kristinsson SY and Cuzick J. Incidence of multiple myeloma in Great Britain, Sweden, and Malmo, Sweden: the impact of differences in case ascertainment on observed incidence trends. BMJ Open 2016; 6: e009584.

[5] Noone AM, Cronin KA, Altekruse SF, Howlader N, Lewis DR, Petkov VI and Penberthy L. Cancer incidence and survival trends by subtype using data from the surveillance epidemiology and end results program, 1992-2013. Cancer Epidemiol Biomarkers Prev 2017; 26: 632-641.

[6] Barwick BG, Neri P, Bahlis NJ, Nooka AK, Dhodapkar MV, Jaye DL, Hofmeister CC, Kaufman JL, Gupta VA, Auclair D, Keats JJ, Lonial S, Vertino PM and Boise LH. Multiple myeloma immunoglobulin lambda translocations portend poor prognosis. Nat Commun 2019; 10: 1911.

[7] Perrot A, Lauwers-Cances V, Tournay E, Hulin C, Chretien ML, Royer B, Dib M, Decaux O, Jaccard A, Belhadj K, Brechignac S, Fontan J, Voillat L, Demarquette H, Collet P, Rodon P, Sohn C, Lifermann F, Orsini-Piocelle F, Richez V, Mohty M, Macro M, Minvielle S, Moreau P, Leleu X, Facon T, Attal M, Avet-Loiseau H and Corre J. Development and validation of a cytogenetic prognostic index predicting survival in multiple myeloma. J Clin Oncol 2019; 37: 1657-1665.

[8] Manier S, Salem KZ, Park J, Landau DA, Getz G and Ghobrial IM. Genomic complexity of multiple myeloma and its clinical implications. Nat Rev Clin Oncol 2017; 14: 100-113.

[9] Shaughnessy JD, Barlogie B and Zhan F. Diagnosis, prognosis and identification of potential therapeutic targets of multiple myeloma based on gene expression profiling. U.S. Patent 9574238 2017.

[10] Lammers E, Cuenca M, Bloem A, Minnema M and Jak M. CD38 and CD45 expression on plasma cells and response to daratumumab in multiple myeloma. Cl Lymph Myelom Leuk 2019, 19: e164.

[11] Zeng Y, Gao L, Luo X, Chen Y, Kabeer MH, Chen X, Stucky A, Loudon WG, Li SC, Zhang X and Zhong JF. Microfluidic enrichment of plasma cells improves treatment of multiple myeloma. Mol Oncol 2018; 12: 1004-1011.

[12] Rheinlander A, Schraven B and Bommhardt U. CD45 in human physiology and clinical medicine. Immunol Lett 2018; 196: 22-32.

[13] Gonsalves WI, Timm MM, Rajkumar SV, Morice WG, Dispenzieri A, Buadi FK, Lacy MQ, Dingli D, Leung N, Kapoor P, Kyle RA, Gertz MA and Kumar SK. The prognostic significance of CD45 expression by clonal bone marrow plasma cells in patients with newly diagnosed multiple myeloma. Leuk Res 2016; 44: 32-39.

[14] Hagen PA, Adams W, Tsai SB, Smith SE, Simms PP and Stiff PJ. Relationship between disease activity and circulating endothelial and endothelial progenitor cells in multiple myeloma. J Clin Oncol 2018; 36: e20004.

[15] Kumar S, Rajkumar SV, Kimlinger T, Greipp PR and Witzig TE. CD45 expression by bone marrow plasma cells in multiple myeloma: clinical and biological correlations. Leukemia 2005; 19: 1466-1470.

[16] Giralt S, Stadtmauer EA, Harousseau JL, Palumbo A, Bensinger W, Comenzo RL, Kumar S, Munshi NC, Dispenzieri A, Kyle R, Merlini G, San Miguel J, Ludwig H, Hajek R, Jagannath S,

Blade J, Lonial S, Dimopoulos MA, Einsele H, Barlogie B, Anderson KC, Gertz M, Attal M, Tosi P, Sonneveld P, Boccadoro M, Morgan G, Sezer O, Mateos MV, Cavo M, Joshua D, Turesson I, Chen W, Shimizu K, Powles R, Richardson PG, Niesvizky R, Rajkumar SV and Durie BG; IMWG. International myeloma working group (IMWG) consensus statement and guidelines regarding the current status of stem cell collection and high-dose therapy for multiple myeloma and the role of plerixafor (AMD 3100). Leukemia 2009; 23: 1904-12.

[17] Hatswell AJ, Burns D, Baio G and Wadelin F. Frequentist and Bayesian meta-regression of health state utilities for multiple myeloma incorporating systematic review and analysis of individual patient data. Health Econ 2019; 28: 653-665.

[18] Gong CL, Studdert AL and Liedtke M. Daratumumab vs pomalidomide for the treatment of relapsed/refractory multiple myeloma: a cost-effectiveness analysis. Am J Hematol 2019; 94: E68-E70.

[19] Gao W, Li J, Jian Y, Yang GZ, Wu Y, Li YC, Len Y, Liu AJ, Tian Y, Wang HJ, Zhou HX, Zhang ZY and Chen WM. Immunoparesis in symptomatic multiple myeloma at diagnosis affects PFS with bortezomib-containing induction therapy, but not ASCT consolidation. Int J Hematol 2019; 109: 169-174.

[20] Richardson PG, Mitsiades C, Ghobrial I and Anderson K. Beyond single-agent bortezomib: combination regimens in relapsed multiple myeloma. Curr Opin Oncol 2006; 18: 598-608.

[21] Graziani MS and Lippi U. Multiple myeloma with serum IgM kappa and Bence Jones lambda biclonal gammopathy. Clin Chem 1986; 32: 2220-2221.

[22] Brudno JN, Maric I, Hartman SD, Rose JJ, Wang M, Lam N, Stetler-Stevenson M, Salem D, Yuan C, Pavletic S, Kanakry JA, Ali SA, Mikkilineni L, Feldman SA, Stroncek DF, Hansen BG, Lawrence J, Patel R, Hakim F, Gress RE and Kochenderfer JN. T cells genetically modified to express an anti-b-cell maturation antigen chimeric antigen receptor cause remissions of poor-prognosis relapsed multiple myeloma. J Clin Oncol 2018; 36: 2267-2280.

[23] Oka S, Ono K and Nohgawa M. Clinical effects of CD45 on the prognosis of extramedullary myeloma relapse. J Clin Pharm Ther 2020; 45: 144-151.

[24] Flores-Montero J, de Tute R, Paiva B, Perez JJ, Bottcher S, Wind H, Sanoja L, Puig N, Lecrevisse Q, Vidriales MB, van Dongen JJ and Orfao A. Immunophenotype of normal vs. myeloma plasma cells: toward antibody panel specifications for MRD detection in multiple myeloma. Cytometry B Clin Cytom 2016; 90: 61-72.

[25] Moreau P, Robillard N, Avet-Loiseau H, Pineau D, Morineau N, Milpied N, Harousseau JL and Bataille R. Patients with CD45 negative multiple myeloma receiving high-dose therapy have a shorter survival than those with CD45 positive multiple myeloma. Haematologica 2004; 89: 547-551.

[26] Iriyama N, Miura K, Hatta Y, Kobayashi S, Uchino Y, Kurita D, Sakagami H, Takahashi H, Sakagami M, Kobayashi Y, Nakagawa M, Ohtake S, Iizuka Y and Takei M. Clinical effect of immunophenotyping on the prognosis of multiple myeloma patients treated with bortezomib. Oncol Lett 2017; 13: 3803-3808.

[27] Brown R, Yang S, Weatherburn C, Gibson J, Ho PJ, Suen H, Hart D and Joshua D. Phospho-flow detection of constitutive and cytokine-induced pSTAT3/5, pAKT and pERK expression highlights novel prognostic biomarkers for patients with multiple myeloma. Leukemia 2015; 29: 483-490.

[28] Lin H, Kolosenko I, Bjorklund AC, Protsyuk D, Osterborg A, Grander D and Tamm KP. An activated JAK/STAT3 pathway and CD45 expression are associated with sensitivity to Hsp90 inhibitors in multiple myeloma. Exp Cell Res 2013; 319: 600-611.

[29] Hillengass J, Usmani S, Rajkumar SV, Durie BGM, Mateos MV, Lonial S, Joao C, Anderson KC, García-Sanz R, Riva E, Du J, van de Donk N, Berdeja JG, Terpos E, Zamagni E, Kyle RA, San Miguel J, Goldschmidt H, Giralt S, Kumar S, Raje N, Ludwig H, Ocio E, Schots R, Einsele H, Schjesvold F, Chen WM, Abildgaard N, Lipe BC, Dytfeld D, Wirk BM, Drake M, Cavo M, Lahuerta JJ and Lentzsch S. International myeloma working group consensus recommendations on imaging in monoclonal plasma cell disorders. Lancet Oncol 2019; 20: e302-e312.

[30] Li J, Stagg NJ, Johnston J, Harris MJ, Menzies SA, DiCara D, Clark V, Hristopoulos M, Cook R, Slaga D, Nakamura R, McCarty L, Sukumaran S, Luis E, Ye Z, Wu TD, Sumiyoshi T, Danilenko D, Lee GY, Totpal K, Ellerman D, Hotzel I, James JR and Junttila TT. Membrane-proximal epitope facilitates efficient t cell synapse formation by anti-FcRH5/CD3 and is a requirement for myeloma cell killing. Cancer Cell 2017; 31: 383-395.

[31] Okamura S, Osaki T, Nishimura K, Ohsaki H, Shintani M, Matsuoka H, Maeda K, Shiogama K, Itoh T and Kamoshida S. Thymidine kinase-1/CD31 double immunostaining for identifying activated tumor vessels. Biotech Histochem 2019; 94: 60-64.

[32] Ouyang J, Li JX, Liu Y and Wu PH. Expression of CD45 and CD31 in differentiation stages of multiple myeloma. Chin J Pathophysiol 2011; 02.