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Prognostic value of expression of CD45 and CD49d in newly diagnosed of multiple myeloma

Kazuhito SUZUKI[1], Shingo YANO[1], Takaki SHIMADA[1], Yuichi YAHAGI[1], Yoji OGASAWARA[1], Katsuki SUGIYAMA[1], Shinobu TAKAHARA[1], Takeshi SAITO[1], Kinuyo KASAMA[1], Hiroki YOKOYAMA[1], Yutaro KAMIYAMA[1], Yumiko INUI[1], Ken KAITO[2], Nobuaki DOBASHI[1], Noriko USUI[1,3] and Keisuke AIBA[1]

The predictive value of surface antigens has still remained controversial after bortezomib was approved. We retrospectively analyzed patients with newly diagnosed multiple myeloma from January 2005 to June 2012 in our department. We focused on two types of surface antigen, CD45 and CD49d, in CD38-positive myeloma cells. Overall survival (OS) was calculated by the Kaplan-Meier method. Prognostic factors for OS were evaluated by Cox regression analysis. Thirty-seven patients were enrolled into this study. The median follow-up time was 20.2 months. There tended to be a difference of OS among four groups, CD45–CD49d+, CD45+CD49d+, CD45–CD49d–, and CD45+CD49d– (log-rank test; $p = 0.051$). Patients were classified into two groups based on the expression patterns of CD45 and CD49d. While median OS in CD45–CD49d+ patients was not reached yet, median OS in non-CD45–CD49d+ patients was 25.2 months (95% CI, 14.6–35.8 months), respectively (log-rank test; $p = 0.014$). Multivariate analysis revealed that CD45–CD49d+ was the independent prognostic factor for longer survival (hazard ratio 0.064. 95% CI 0.006–0.643; $p = 0.020$). In conclusion, the expressions of CD45–CD49d+ seemed to be a favorite OS in multiple myeloma patients.

Key words: multiple myeloma, CD45, CD49d, flow cytometry, bortezomib, CAM-DR

Introduction

Multiple myeloma is characterized by a clonal human plasma cell neoplasm and develops mainly in bone marrow. Myeloma cells appear to be heterogeneous in terms of the expression of surface antigens and biological characteristics [1]. Analysis of surface antigens by flow cytometry (FCM) had been reported as one of predictors for prognosis before bortezomib became available [2]. But, the predictive value of surface antigens has been controversial in the era of bortezomib.

During plasma cell development, it has been well-known that progressive loss of B-cell markers, such as CD19 and CD20, and the acquisition of markers, such as CD138 and CD56, confer malignant phenotype on plasma cells [3]. CD45 is the leukocyte common antigen and can be found on all hematopoietic cells but not on red blood cells or platelets [3]. Most of myeloma cells do not express CD45, but immature proliferating myeloma cells express CD45 [2]. Kumar S *et al.* had reported that the median overall survival (OS) in CD45+ patients tended to be longer than that in CD45– patients [4]. CD49d is a subunit of very late antigen-4 (VLA-4), which was identified as a critical molecule for the induction of cell adhesion-mediated drug resistance (CAM-DR). The interaction between myeloma cells and neighboring stromal cells which express vascular cell adhesion molecule-1 (VCAM-1) enhances the production of factors for osteoclastogenesis, and the disruption of this cell-to-cell contact by neutralizing antibody against VCAM-1 suppresses osteoclastogenic activity [5,6]. Myeloma patients with primary multidrug resistance showed significantly higher

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[1] Division of Clinical Oncology/Hematology, Department of Internal Medicine, the Jikei University School of Medicine
[2] Central Clinical Laboratory, the Jikei University Hospital
[3] Division of Transfusion Medicine, the Jikei University School of Medicine

Corresponding author: Keisuke AIBA
Division of Clinical Oncology/Hematology, The Jikei University School of Medicine, 3-25-8 Nishi-Shinbashi, Minato-ku, Tokyo 105-8461, Japan
TEL: 81-3-3433-1111, FAX: 81-3-3436-3233
E-mail: aiba@jikei.ac.jp

concentrations of serum VLA-4 and intercellular adhesion molecule-1 (ICAM-1) than those with the higher sensitivity to anti-myeloma drugs [7]. However, *in vitro* analyses showed that bortezomib may be effective in ameliorating CAM-DR through downregulation of VLA-4 expression in myeloma cells [8].

We analyzed the expression of CD45 and CD49d on multiple myeloma cells at initial diagnosis. The purpose of this retrospective study was to investigate the prognostic value of these surface antigens.

Methods

Patients

We retrospectively analyzed thirty-seven patients with newly diagnosed multiple myeloma from January 2005 to June 2012 at the Jikei University Hospital. This study was approved by the Independent Ethics Committee/Institutional Review Board in our institute. Patients provided written informed consent before entering the studies, which were carried out in accordance with the Declaration of Helsinki. Median age was 65 (range: 51–88) years old and all patients had symptomatic multiple myeloma. Symptomatic multiple myeloma was defined by serum monoclonal protein ≥3 g/dL or bone marrow plasma cells ≥10% with any of the CRAB (CRAB; calcium elevation, renal insufficiency, anemia and bone disease) criteria, such as an elevation of serum calcium (>11.5 mg/dL), renal insufficiency (serum level of creatinine >2 mg/dL), anemia (hemoglobin concentration <10 g/dL or 2 g/dL less than the lower normal limit) and lytic or osteopenic bone disease [9].

Treatment and assessment of response

All patients received standard regimens of induction therapy, such as bortezomib plus dexamethasone (BD), vincristine, adriamycin plus dexamethasone (VAD), melphalan plus predonisolone (MP), or high-dose dexamethasone (HDD). Eight patients received high-dose melphalan followed by autologous peripheral blood stem cell transplantation. Patients who relapsed or had refractory disease received salvage therapy of BD, cyclophosphamide, bortezomib plus dexamethasone (CVD), melphalan, bortezomib plus predonisolone (MBP), bortezomib, lenalidomide plus dexamethasone (BLD), lenalidomide plus low-dose dexamethasone (Ld), thalidomide plus dexamethasone (TD), ranimustine, vincristine, melphalan plus dexamethasone (ROAD), MP, HDD, or VAD. Evaluation of response was carried out based on the following criteria. Complete response (CR) was defined as having negative serum/urine immunofixation, the disappearance of any soft tissue plasmacytomas and ≤5% plasma cells in bone marrow. Very good partial response (VGPR) was defined as having serum/urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein <100 mg per 24 hours. Partial response (PR) was defined as having ≥50% reduction of serum M-protein and reduction of 24-hour urinary M-protein by ≥90% or to <200 mg per 24 hours. Progressive disease (PD) was defined as >25% increase in M-protein on two separate measurements at 4-week intervals. Stable disease (SD) was not meeting the criteria for CR, VGPR, PR, or PD [10].

Flow cytometry analysis

FCM analysis was performed in the single laboratory at Special Reference Laboratories, Inc. (SRL, Tokyo Japan). Two types of antibodies were used: CD45 and CD49d for CD38 positive cells. These expressions were evaluated by two-color panel of antibodies.

Statistical analysis

OS was defined as time from diagnosis to death resulting from any cause. Univariate analysis was performed for each of the parameters indicated above. OS was analyzed by using Kaplan-Meier methodology, and differences of OS between groups were assessed with the log-rank test. We analyzed prognostic factors for OS, such as surface antigens, age, anemia by the CRAB criteria, renal failure by the CRAB criteria, the International Staging System (ISS) [11], cytogenetic abnormality, bortezomib containing induction therapy, and autologous stem cell transplantation, using Cox regression analysis. The chi-square and Fisher's exact tests were used to compare differences between two groups. All *p*-values were two-sided, and statistical significance was defined as $p < 0.05$. The statistical analyses were computed with SPSS statistical software (SPSS Inc., Chicago, IL).

Results

Patients

We analyzed thirty-seven patients with multiple myeloma. The patient characteristics are shown in Table 1. The classification of the ISS was as follows: 9 had ISS 1, 17 had ISS 2, 8 had ISS 3, and 3 had no available data. Nine patients had cytogenetic abnormality by Q bands analysis, 7 had hyperdiploid, 1 had hypodiploid, 1 had t(11;14), 1 had del(17), and 2 had –Y.

Flow cytometry analysis

Plasma cells were identified by strong expression of CD38. Among thirty-seven patients, the median percentages of CD19, CD45, CD49d, CD49e, and CD56 positive cells were 2.0% (range, 0.1–63.9%), 22.6% (range, 0.9–100), 86.9% (range, 0.7–99.2), 1.7% (range, 0.0–47.7), and 87.5% (range, 1.2–99.7),

Table 1. Patient characteristics

	All patients	CD45–CD49d+	CD45+CD49d+ CD45–CD49d– CD45+CD49d–	*P* value
Age				
Median		65 yr (51–87)		
≤65 yr	24	10	14	.387
>65 yr	13	4	9	
Gender				
male	20	7	13	.481
female	17	7	10	
M protein subtype				
IgG	24	7	17	.092
IgA	6	3	3	
BJP	6	4	2	
others	1	0	1	
International Staging System				
1	9	3	6	.598
2	17	6	11	
3	8	3	5	
NA	3	2	1	
Anemia according to CRAB criteria				
positive	28	12	16	.241
negative	9	2	7	
Renal failure according to CRAB criteria				
positive	3	0	3	
negative	34	14	20	
Serum level of LDH				
>UNL	5	3	2	.269
≤UNL	32	11	21	
Serum level of CRP				
>UNL	20	8	12	.519
≤UNL	17	6	11	
Bortezomib containing Induction Therapy				
Yes	9	3	6	.536
No	28	11	17	
MP	18	6	12	
VAD	7	4	3	
HDD	3	1	2	
Autologous stem cell transplant				
Yes	7	4	3	.228
No	30	10	20	
Cytogenetics				
normal	22	7	15	.204
abnormal*	9	4	5	
NA	6	2	4	

* Cytogenetic abnormality by Q-binding method were 7 of hyperdiploid, 1 of hypodiploid, 1 of t(11;14), 1 of del17, and –Y; 2.
BJP; Bence Jones protein, NA; not available, ISS; International Staging System, CRAB; calcium elevation, renal insufficiency, anemia and bone disease, LDH; lactase dehydrogenase, CRP; C-reactive protein, MP; melphalan plus predonisolone, VAD; vincristine, adriamycin plus dexamethasone, HDD; high-dose dexamethasone, UNL; upper normal limit, NA; not available.

respectively. We focused on the correlation between OS and the expressions of CD45 and CD49d. In this study, the cut-off levels for CD45 positivity and CD49d positivity were defined as 20% and 50%, respectively. Eighteen out of 37 patients had CD45+ plasma cells. Thirty patients expressed CD49d+ and 7 had CD49d–.

Table 2. Chemotherapy and response

	All patients	CD45–CD49d+	CD45+CD49d+ CD45–CD49d– CD45+CD49d–	*P* value
Response by Induction Therapy				
PR or better	19	8	11	.233
SD or less	13	3	10	
CR	0	0	0	
VGPR	6	4	2	
PR	13	4	9	
SD	10	1	9	
PD	3	2	1	
NA	2	2	0	

PR; partial response, SD; stable disease, CR; complete response, VGPR; very good partial response, PD; progression disease, NA; not available.

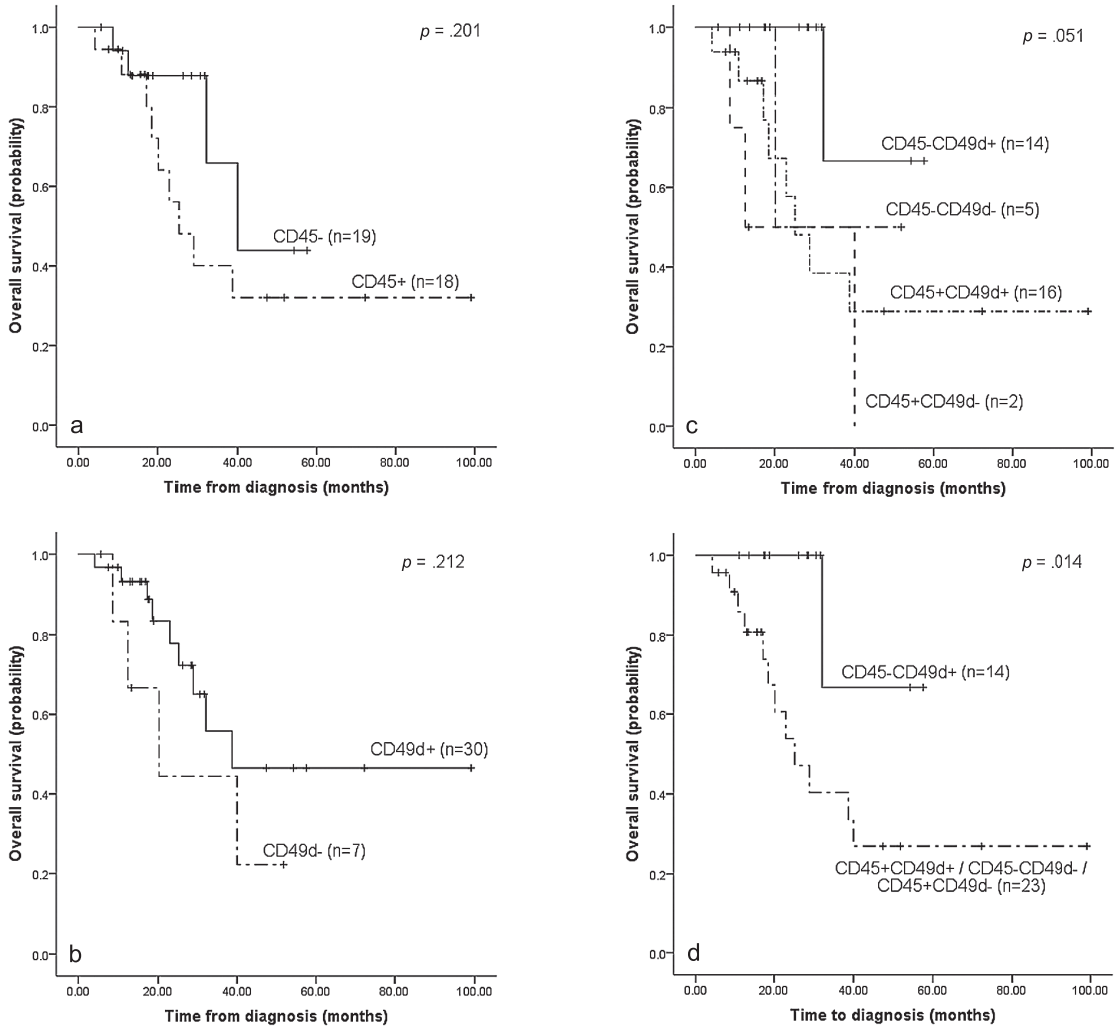

Figure 1. a. The overall survival in CD45+ patients and CD45– patients. There was no significant difference in overall survival between CD45+ patients and CD45– patients (p = 0.201). b. The overall survival in CD49d+ patients and CD49d– patients. There was no significant difference in overall survival between CD49d+ and CD49d– (p = 0.212). c. The overall survival in CD45–CD49d+ patients, CD45+CD49d+ patients, CD45–CD49d– patients, and CD45+CD49d– patients. There tended to be significant difference of overall survival in four groups, CD45–CD49d+ patients, CD45+CD49d+ patients, CD45–CD49d– patients, and CD45+CD49d– patients (log-rank test; p = 0.051). d. The overall survival in CD45–CD49d+ patients compared with those in CD45+CD49d+ patients, CD45–CD49d– patients, and CD45+CD49d– patients. Overall survival in CD45–CD49d+ patients was significantly longer than those in CD45+CD49d+ patients, CD45–CD49d– patients, and CD45+CD49d– patients (log-rank test; p = 0.014).

Table 3. The multivariate analyses for overall survival

Factor	Hazard ratio (range)	*P* value
CD45– and CD49d+	.064 (.006–.643)	.020
CD45+CD49d+, CD45–CD49d–, CD45+CD49d–	1.0	
Age > 65 yr	.985 (.167–5.804)	.986
Age ≤ 65 yr	1.0	
Anemia by CRAB criteria	3.299 (.511–21.299)	.210
non-anemia by CRAB criteria	1.0	
Renal failure by CRAB criteria	NA	.990
non-renal failure by CRAB criteria	1.0	
ISS 3	2.351 (.191–28.959)	.505
ISS 1, 2	1.0	
Cytogenetic abnormality positive	1.380 (.212–8.978)	.736
Cytogenetic abnormality negative	1.0	
Bortezomib containing Induction Therapy	2.185 (.176–27.115)	.543
non-Bortezomib containing Induction Therapy	1.0	
Autologous stem cell transplant	.683 (.096–4.834)	.702
non-Autologous stem cell transplant	1.0	

CRAB; calcium elevation, renal insufficiency, anemia and bone disease, ISS; international staging system, NA; not available.

Response to induction therapy

Response to induction therapy is shown in Table 2. As induction therapy, nine patients received BD, 18 MP, 7 VAD, and 3 HDD. Overall response rates of all patients and the patients who received BD were 51.4% and 66.7%, respectively. Three patients discontinued induction therapy: 1 was because of peripheral neuropathy due to BD, 1 was respiratory failure due to MP, and 1 was poor performance status due to MP. Seven patients received autologous stem cell transplant when the patients had obtained equal to or better than PR.

Survival

Median follow-up time was 20.2 months (range, 4.2–99.1). First, we compared OS between CD45+ patients and CD45– patients, and between CD49d+ and CD49d–. There were no significant difference of OS between CD45+ patients and CD45– patients, and between CD49d+ and CD49d–, respectively ($p = 0.201$, and 0.212, Fig. 1a, 1b). Next, we evaluated OS in respective four groups, CD45–CD49d+, CD45+CD49d+, CD45–CD49d–, and CD45+CD49d– patients. There tended to exist different OS among four groups (log-rank test; $p = 0.051$, Fig. 1c). The survival of CD45–CD49d+ patients tended to be better than the others, and OS in CD45–CD49d+ patients was significantly better than those in non-CD45–CD49d+ patients ($p = 0.014$, Fig. 1d). Median OS in CD45–CD49d+ patients was not reached, but median OS in non-CD45–CD49d+ patients was 25.2 months.

Multivariate analysis of the seven prognostic factors, such as age, anemia by the CRAB criteria, renal failure by the CRAB criteria, ISS, cytogenetic abnormality, bortezomib containing induction therapy, and autologous stem cell transplantation, in this model demonstrated that CD45–CD49d+ was an independent prognostic factor for OS (hazard ratio 0.064. 95% CI 0.006–0.643; $p = 0.020$) (Table 3).

Discussion

This study suggested that OS was significantly better in the patients with CD45–CD49d+ on myeloma cells. Several well-known prognostic predictors of newly diagnosed multiple myeloma have been ISS[11], Durie and Salmon system[12], abnormal cytogenetics[13–18], and gene expression profiling[19,20]. However, the prognostic values of surface antigens have been controversial since bortezomib was approved.

CD45 is a leukocyte common antigen expressed on all hematopoietic cells except for both mature erythrocytes and platelets. CD45 molecule is expressed on all nucleated hematopoietic cells, whereas the expression of CD45 molecules on primary myeloma cells and cell lines is quite variable, a finding consistent with the heterogeneity of myeloma cells[21]. Human myeloma cells isolated from patients are potent in responding to cytokines, including interleukin-6 (IL-6), and are able to proliferate in *in vitro*[22]. The CD45+ myeloma cells appear to be more proliferative in response to IL-6 than CD45– cells[2,23,24]. In addition, IL-6 modulates the expression of CD45 on myeloma cells[23]. Kumar S *et al*. reported that CD45+

cells increased significantly in patients with monoclonal gammopathy of undetermined significance (MGUS) and smoldering myeloma compared with those in newly diagnosed myeloma and relapsed myeloma cells. Median OS in CD45+ patients tended to be longer than that in CD45– patients[4]. These differences of OS in our result and the previous report were not significant. Moreover, in our patients, there was no significant difference in overall response rate between CD45+ and CD45– patients ($p = 0.630$).

CD49d is a subunit of VLA-4, a heterodimer of CD49d/CD29. VLA-4 is an unusual β1 integrin expressed on resting lymphocytes, monocytes and neural crest-derived cells, and functions as both a matrix and cell receptor. VLA-4 binds to molecules such as VCAM-1, which is a member of the immunoglobulin superfamily. VCAM-1 is induced by inflammatory mediators on the endothelium with kinetics similar to ICAM-1, and interaction with VLA-4 provides an explanation for the earlier evidence of a second lymphocyte-endothelium adhesion mechanism distinct from the LFA-1/ICAM interaction[25]. VLA-4-mediated signaling is important for the development of *in vitro* CAM-DR in myeloma cells[26]. It has been reported that myeloma patients with primary multidrug resistance showed significantly higher serum concentration of VLA-4 and ICAM-1 than those with responders[6]. Moreover, administration of anti-α4 integrin antibody suppressed the growth of myeloma cells in a murine xenograft[27,28]. It has been reported that bortezomib overcomes CAM-DR through downregulation of the expression of CD49d, a subunit of VLA-4 in *in vitro*[7,29]. However, there has been no data that bortezomib could overcome CAM-DR *in vivo*. In our patients, there was no significant difference between expression of CD49d and response rate by bortezomib containing regimens as induction therapy. High CD49d expression was not associated with a poor response ($p = 0.233$). Thus, CAM-DR might not be identified among patients with CD49d+ in *in vivo*.

In this study, the cut-off levels for CD45 positivity and CD49d positivity were defined as 20% and 50%, respectively. We defined as the cut-off of CD45 positivity as 20% according to previous reports. However, only two patients had CD49d positive plasma cells in case the cut-off level of CD49d positivity was defined as 20%. Median percentage of CD49d positivity was 86.9% in all patients and the percentage of CD49d positive plasma cells was 50% or more among the majority of patients. Therefore, we defined as the cut-off level of CD49d positivity as 50%.

In our patients, CD45–CD49d+ patients significantly survived longer than non-CD45–CD49d+ patients, while there were no significant difference in overall response rate between CD45–CD49d+ and non-CD45–CD49d+ patients ($p = 0.233$). Moreover, the response duration in the patients with CD45– and CD49d+ tended to be longer than that in the patients without CD45+ and CD49d– ($p = 0.074$). In multivariate analysis, the phenotype of CD45–CD49d+ was a favorable prognostic factor for OS. In this study, a total of 13 patients died and the causes of death were myeloma in 8, amyloidosis in one, sepsis in one, liver failure in one, hypoglycemia in one, and unknown in one. In the CD45–CD49d+ group, only 1 patient died of myeloma, while in the non-CD45–CD49d+ group, deaths from other causes than myeloma were observed. This might contribute to short-term survival in the non-CD45–CD49d+ group. In addition, we analyzed morphological findings in twelve bone marrow samples according to the Griepp's criteria. Unfortunately, the other twenty-five bone marrow samples were not available (due to a huge earthquake in March 2011). In patients with CD45–CD49d+ myeloma cells, three patients had mature myeloma cells, and three had immature myeloma cells. In patients without CD45–CD49d+ myeloma cells, three patients had mature myeloma cells, one had intermediate myeloma cells, one had immature myeloma cells, and one had blastic myeloma cells. There were no significant correlation between CD45–CD49d+ positivity and myeloma cell morphology according to the Griepp's criteria ($p = 0.716$). Finally, the average level of serum creatinine in non-CD45–CD49d+ arm was higher than that in CD45–CD49d+ arm (0.99 mg/dL vs 1.70 mg/dL, $p = 0.048$) by t-test. The average level of serum beta2-microgloburin in non-CD45–CD49d+ arm tended to be higher than CD45–CD49d+ arm (4.4 mg/dL vs 6.4 mg/dL, $p = 0.074$) by t-test. The patients with CD45–CD49d+ myeloma cells might be better renal function than those without CD45–CD49d+ myeloma cells. However, our trial was a small retrospective trial and the results were therefore limited. Possibility of the prognostic value of expressions of CD45 and CD49d on myeloma cells need to be necessary to be investigated on a well-designed large clinical trial.

In conclusion, the expression of CD45–CD49d+ by FCM might be predictive factor for a favorite outcome among patients with multiple myeloma. However, our sample size was small, and larger-scale research would be needed to confirm prognostic value of expression of CD45 and CD49d in myeloma patients.

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Conflict of Interest

The authors declared no potential conflicts of interest.

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