Lack of CD45 and CD56 expression implies bad prognosis in multiple myeloma patients

Omnia Abd-Elfattah M.D.[1], Nashwa Noreldin M.D.[2], Mohamed Attia M.D.[3]

Departments of [1]Clinical Oncology, [2]Internal Medicine and [3]Clinical Pathology, College of Medicine, University of Tanta, Tanta, Egypt
omniaabdelfattah@yahoo.com

Abstract: Background: contradictory results have been shown concerning the significance of negative CD45 and CD56 expression on prognosis in multiple myeloma (MM) patients. Discrepancy of results has been at times claimed to be due to the possible impact of used high dose chemotherapy on disease progress. In this study, we have analyzed the significance of negative CD45 or CD56 expression on response to treatment and survival in non transplant-eligible MM patients not exposed to high dose chemotherapy **Methods:** Fifty six newly diagnosed, symptomatic non transplant eligible MM patients were enrolled in this observational cohort prospective study. All patients treated with vincristine, adryamicin and dexamethasone (VAD) regimen as a conventional chemotherapy. Myeloma work-up included bone marrow examination, skeletal survey, serum β_2-microglobulin level, serum protein electrophoresis (SPE),serum immunofixation, CBC, serum albumin, calcium,C reactive protein, creatinine and LDH. Staging was performed according to the international staging system (ISS), bone marrow cellularity, percentage of plasma cells and percent of CD45,CD 56 on bone marrow cells by flowcytometry. **Results:** Significantly less complete remission (CR) and more partial remission (PR) and stable disease (SD) in CD45-ve compared to CD45+ve patients (P=0.001) whereas patients with CD56-ve expression showed less CR, more PR and equal SD compared to CD56+ve (P =0.002). The median overall survival (OS) and event free survival (EFS) for all patients were 23 and 21 months. The median OS and EFS were significantly less in patients with CD45-ve compared to CD45+ve (18 vs 23 P=0.029) and in CD56-ve compared to CD56 +ve (11 vs 23 P=0.000). **Conclusion:** Absence of CD56 and/or CD45 expression on bone marrow plasma cells in non transplant eligible MM patients treated with VAD is associated with inferior prognosis.

[Omnia Abd-Elfattah, Nashwa Noreldin, Mohamed Attia. **Lack of CD45 and CD56 expression implies bad prognosis in multiple myeloma patients**. *Life Sci J* 2013;10(4):1526-1533]. (ISSN: 1097-8135). http://www.lifesciencesite.com. 201

Keywords: CD45, CD56, multiple myeloma, prognosis.

1. Introduction

Multiple myeloma cells present a heterogeneous expression pattern with a mixture of negative and positive CD45 and CD56 [1-3]. The CD45 negative phenotype was shown to reflect the phenotype of progressive disease in relation to the intrinsic malignancy of the MM clone[4]. Also, lack of CD56 expression has been correlated with κ Bence Jones myeloma [5] and low osteolytic potential myeloma[6], and bad prognosis with higher rate of extramedullary involvement and renal insufficiency[7]. On the other hand, other studies [4,8] showed that lack of CD56 and CD45 expressions carry no distinct adverse prognosis and do not define a unique clinicopathological or prognostic entity. It was thought [9] that the bad prognostic impact of –ve CD45 and CD56 expression might be overwhelmed by the effect of high dose chemotherapy used in transplant eligible patients.

In this study, we will try to find out the relationship between lack of CD45 or CD56 expression on disease characteristics and prognosis in non-eligible MM patients in absence of high dose chemotherapy drug action.

2. Patients and methods

In this observational prospective cohort study, 56 newly diagnosed symptomatic non transplant eligible MM patients with different CD45 and CD56 expressions were identified and observed over time, and the OS and EFS were measured and compared. Patients were treated and followed up at Tanta Hospital of the University, Egypt during the period from June 2010 to December 2012. Written, informed consent was obtained from all patients before enrollment into the study.

Laboratory investigations, Staging and Flowcytometry

Work-up included bone marrow examination, skeletal survey, serum β_2-microglobulin level, SPE, serum immunofixation, complete blood picture, serum albumin, calcium, C reactive protein, creatinine and LDH. Patients were clinically staged according to ISS [10]. Bone marrow examination included cellularity, percentage of plasma cells. Examination of bone marrow cells by flowcytometry was done by separating mononuclear cells (MNCs) using density gradient. Ficoll-Paque. MNcs were labelled with PE-labelled anti-CD38 PerCp -Labelled anti- CD45, APC-labelled

anti- CD138 and FITC-labelled anti- CD56. All monoclonal antibodies were supplied by BD (Ten microlittres of each antibody) or its matching isotype control (was added to the 5x10 5cells and incubated for 30 minutes on ice in the dark. The cells were washed twice in PBS containing 1% BSA and finally were resuspended in 1% formaldehyde and analyzed on a FACS Calibur flow cytometer with Cell Quest (Pro Software Becton Dickinson). Data acquisition was always performed in two steps: first, 15,000 total cells were collected, second, at least 1,000 PC were acquired with an activated live gate on SSC versus CD38 (strongly positive) dot plot and PC were identified double positivity for CD38 and CD138. CD45 and CD56 expressions were analyzed on PC and displayed in dot plot format. The cut off for positivity was arbitrary set at or more than 20%. Protein electrophoresis and immunofixation were done using agarose gel electrophoresis and antibodies provided by Hellabio (Greece). Serum β_2-microglobulin was measured using ELISA kit (ab99977) from Abcam, USA supplied by KEMET Medical Egypt.

Therapy: Cardiac examination was carried out before each cycle. All patients were treated with VAD regimen as a frontline chemotherapy [11]. Those with serious concurrent medical conditions that precluded the use of high-dose dexamethasone were not included in our study. They received a continuous infusion of vincristine 0·4 mg/d and doxorubicin 9 mg/m2/d. Dexamethasone was administered i.v. from days 1 to 4 (40 mg/d). During the first two cycles, the same dose of dexamethasone was administered orally from days 9 to 12 and from days 17 to 20. The patients were hospitalized for the first 4 days of each cycle. The treatment cycles were repeated at 4-weeks intervals. With the first VAD patients were given allopurinol 300 mg daily for 2 weeks. Prophylaxis was routinely given against infection: cotrimoxazole 450 mg twice daily and ketoconazole 400 mg daily. Cimetidine 400 mg twice daily was used as prophylaxis for steroid-induced dyspepsia. All agents were given for 7 days every time patients commenced dexamethasone. Patients with myeloma-related bone disease received bisphosphonate therapy monthly to prevent or delay skeletal events. Radiation therapy to limited areas is indicated to control pain and to prevent or treat spinal cord compression. Orthopedic interventions and/or radiation may also be needed to prevent or treat pathologic fracture in susceptible long bones with large lytic lesions.

Response criteria: Patients' assessment of response was done after six cycles of VAD according to standard published guidlines[12]. CR was defined as complete resolution of disease with absent paraprotein, as evidenced by a negative SPE and immunofixation, and <5% plasma cells in the bone marrow. Partial response (PR) was defined as reduction of paraprotein (>50%), serum M protein and 24 hour urinary M protein by (> 90% or to <200 mg / 24 hour). Progressive disease (PD) (disease progression on or off therapy) required one or more of the following findings: more than 25% increase in the level of the serum monoclonal protein, which must also be an absolute increase of at least 5 g/L and confirmed by at least one repeated investigation, more than 50% increase in the 24-hour urinary light chain excretion confirmed by at least one repeated investigation, definite increase in the size of existing bone lesions or soft-tissue plasmocytomas, development of new bone lesions or soft-tissue plasmacytomas, or development of hypercalcemia not attributable to any other cause.. Stable disease (SD) is that not meeting the criteria for CR, PR or PD. Toxicity and side effects of the study treatment regimen were evaluated after each cycle; Patients who don't respond optimally to VAD are shifted to receive salvage therapy[13] in the form of thalidomide 100 to 200 mg orally at bedtime with serial increments of 50 to 100 mg at weekly intervals, as tolerated to a maximum of 600 mg orally at bed time and received dexamethasone 20 mg/m2 beginning on days 1, 9, and 17; the second and third cycles of repeated dexamethasone were begun on day 30 also warfarin in therapeutic doses was used. OS was defined as time from diagnosis to date of death from any cause or last follow-up. EFS was defined as time from the start of treatment to the date of progression or death [14].

Statistical analysis:

Nonparametric data were expressed as median and interquartile range or median and SE for OS and EFS. Comparison was done using Chi- Square test or Mann–Whitney rank-sum as needed. Survival curves were plotted by Kaplan-Meier method and compared by the log-rank test. Multivariate Cox regression analysis was performed to analyze the impact on OS and EFS of CD45 and CD56. A P value ≤ 0.05 was considered significant. Analysis was performed using Statistical Package for the Social Sciences (SPSS) version16.

3. Results

Follow up range (9-27m) Median 21 m. No significant differences were detected in age and sex of CD45-ve and CD45+ve patients (P =0.887 and 0.842 respectively) whereas significant differences were detected in age and sex of CD56-ve and CD56+ve patients (P<0.001 and 0.005 respectively). Significant differences were detected between IgG, IgA and BJ of CD45-ve and CD45+ve patients (P =0.026) whereas no significant differences were detected in CD56-ve and CD56+ve patients (P <0.559). No significant differences were detected between number of CD45-ve and CD45+ve patients among all ISS stages (P =0.658)

whereas significant difference were detected in CD56-ve and CD56+ve patients (P <0.001). Lytic bone lesions were significantly higher in CD45-ve patients compared to CD45+ve patients whereas they were significantly higher in CD56+ve patients (Table 1). No significant changes were detected in performance status between CD45 –ve or +ve patients whereas it was significantly lower in CD56 +ve patients (Table.1). Flowcytometry image of CD45 and CD56 were shown in Figure 1.

Both CD45 expressions (+ve and –ve) were not associated with significant changes in β_2-microglobulin, serum albumin, hemoglobin, calcium level, C-reactive protein, creatinine level or LDH level (Table 2) whereas lack of CD56 expression was associated with significantly high β_2-microglobulin, low serum albumin, low hemoglobin, high calcium level, high C-reactive protein, high creatinine level and high LDH level ($P \leq 0.001$) (Tables 2,3). Side effects of treatment are shown in Table 4.

Outcome results, after VAD treatment, showed less CR and more PR and SD in CD45-ve compared to CD45+ve patients (P =0.001) whereas patients with CD56-ve expression showed less CR, more PR and equal SD compared to CD56+ve (P =0.002) (table 5). Ten patients needed salvage therapy as 2 of them developed SD while 8 developed PD. Those with PD had CD45-ve expression in 7 patient and CD45+ve expression in 1 patients (P =0.001) while all of them showed -ve expression of CD56 (P =0.032).

The median OS and EFS for all patients were 23 and 21 months respectively (Table 6, Figure 2). The median OS was significantly less inCD45-ve and CD56-ve patients(P = 0.029 and 0.000 respectively) (Table 7, Figures 3). The median EFS was significantly less in CD45-ve and CD56-ve patients (P = 0.0215 and 0.001 respectively) (Table 8, Figure 4).

Both markers (CD 45 and CD 56) were simultaneously positive in 12 patients while were simultaneously negative in 9 patients. The median OS when both markers were negative was 11 months compared to 26.2 months when both markers were positive while the median EFS when both markers were negative was 9 months compared to 18 months when both markers were positive Figure 5.

Table I. patients characteristics at presentation according to CD45 and CD56 expression

		CD45						CD56					
		Negative/ Positive		Total		Chi-Square		Negative/Positive		Total		Chi-Square	
		N	%	N	%	X^2	P-value	N	%	N	%	X^2	P-value
Age	40-60.	10/5	17.86/8.96	15	26.79	0.241	0.887	3/12	5.36/21.43	15	26.79	19.541	<0.001*
	60-70.	24/9	42.86/16.07	33	58.93			3/30	5.36/53.57	33	58.93		
	>70.	6/2	10.71/3.57	8	14.29			7/1	12.5/1.79	8	14.29		
Sex	Male	31/12	55.36/21.43	43	76.79	0.040	0.842	13/30	23.21/53.57	43	76.79	7.985	0.005*
	Female	9/4	16.07/7.14	13	23.21			0/13	0.00/23.21	13	23.21		
M Component Isotype	IgG	19/13	33.93/23.21	32	57.14	7.298	0.026*	7/25	12.50/44.64	32	57.14	1.164	0.559
	IgA	15/1	26.79/1.79	16	28.57			5/11	8.93/19.64	16	28.57		
	(BJ)	6/2	10.7/13.57	8	14.29			1/7	1.79/12.50	8	14.29		
Internationl Staging system	I	15/8	26.79/14.29	23	41.07	0.837	0.658	0/23	0.00/41.07	23	41.07	33.352	<0.001*
	II	14/5	25.00/8.93	19	33.93			2/17	3.57/30.36	19	33.93		
	III	11/3	19.64/5.36	14	25.00			11/3	19.64/5.36	14	25.00		
Lytic bone Lesion	No	1/5	1.79/8.93	6	10.71	9.201	0.010*	0/6	0.00/10.71	6	10.71	6.362	0.042*
	Single	14/3	25.00/5.36	17	30.36			2/15	3.57/26.79	17	30.36		
	Multiple	25/8	44.64/14.29	33	58.93			11/22	19.64/39.29	33	58.93		
Performance status	≤2.	22/9	39.29/16.07	31	55.36	0.007	0.932	4/27	7.14/48.21	31	55.36	4.142	0.042*
	>2.	18/7	32.14/12.50	25	44.64			9/16	16.07/28.57	25	44.64		

N=number; *=significant

Table 2. Laboratory parameters at presentation according to CD56 expression

CD56		Range			Median	Interquartile Range	Mean Rank	Mann-Whitney Test Z	Mann-Whitney Test P-value
β_2-microglobulin(mg|dl)	**Negative**	3.600	-	16.600	7.300	4.350	46.115	-4.446	<0.001*
	Positive	0.800	-	13.200	3.200	2.200	23.174		
Serum albumin(g|l)	**Negative**	1.800	-	3.200	2.800	0.650	14.192	-3.615	<0.001*
	Positive	2.000	-	5.700	3.600	1.100	32.826		
Hemoglobin(g|dl)	**Negative**	5.900	-	9.500	7.200	1.550	13.500	-3.786	<0.001*
	Positive	5.300	-	13.500	9.700	2.200	33.035		
Calcium level(mg|dl)	**Negative**	9.900	-	19.300	14.200	5.050	42.885	-3.631	<0.001*
	Positive	2.500	-	19.900	10.200	4.000	24.151		
C-reactive protein (CRP) (mg|dl)	**Negative**	1.300	-	50.200	27.300	20.400	41.885	-3.379	0.001*
	Positive	0.000	-	48.500	4.500	15.400	24.453		
Creatinne level(mg|dl)	**Negative**	2.000	-	13.900	6.700	7.750	43.308	-3.738	<0.001*
	Positive	0.200	-	13.200	1.800	2.900	24.023		
LDH level U|L	**Negative**	244.000	-	978.000	740.000	408.000	42.192	-3.455	0.001*
	Positive	213.000	-	990.000	265.000	109.000	24.360		

*=significant

Table 3. Laboratory parameters at presentation according to CD 45expression

CD45		Range	Median	Interquartile Range	Mean Rank	Mann-Whitney Test	
						Z	*P*-value
β_2-microglobulin(mg|dl)	Negative	0.800 - 16.600	3.900	3.850	30.063	-1.134	0.257
	Positive	0.900 - 10.100	3.400	3.250	24.594		
Serum albumin(g|l)	Negative	1.800 - 5.700	3.100	1.100	27.612	-0.645	0.519
	Positive	2.200 - 5.500	3.400	1.325	30.719		
Hemoglobin(g|dl)	Negative	5.300 - 13.500	8.800	2.650	26.138	-1.715	0.086
	Positive	6.100 - 13.100	10.050	2.800	34.406		
Calcium level(mg|dl)	Negative	5.900 - 19.300	11.100	4.425	29.400	-0.653	0.514
	Positive	2.500 - 19.900	9.950	9.350	26.250		
C-reactive protein (CRP) (mg|dl)	Negative	0.000 - 50.200	14.700	22.475	30.462	-1.425	0.154
	Positive	0.000 - 48.500	3.700	14.450	23.594		
Creatinne level(mg|dl)	Negative	0.200 - 13.900	2.750	3.900	30.325	-1.325	0.185
	Positive	0.300 - 13.000	1.400	4.225	23.938		
LDH level U|L	Negative	213.000 - 990.000	334.500	496.000	30.913	-1.750	0.080
	Positive	235.000 - 978.000	258.500	111.250	22.469		

Table 4. Side effects after 6 cycles of VAD treatment

Toxicity (Total Number 0f patients=56)	N	%
Nausea and Vomiting	7	12.50
Infection (chest/urinary)	25 (10/15)	44.64
Parathesia	12	21.43
Oral Candidiasis	18	32.14
Dyspepsia	17	30.36
Constipation	11	19.64
Steroid-associated oedema	13	23.21
Heart Failure	1	1.79
(Anemia±thrombocytopenia)	9	16.07

N=number

Table 5. Treatment outcome

Outcome	CD45						CD56					
	Negative		Positive		Chi-Square		Negative		Positive		Chi-Square	
	N	%	N	%	X^2	P-value	N	%	N	%	X^2	*P*-value
CR	7	12.5	12	21.43	17.121	0.001*	0	0.00	19	33.93	12.911	0.002*
PR	31	55.36	4	7.14			12	21.43	23	41.07		
SD	2	3.57	0	0.00			1	1.79	1	1.79		

N=number; CR complete remission; PR partial remission; SD stable disease; *=significant

Table 6. OS and EFS for all patients

All patients	***Median***	***±SE***
OS	***23.00***	***±2.17***
EFS	***21.00***	***±1.50***

SE=standard error

Table 7. OS in relation to CD 45,CD 56

	CD 45		CD56	
	Median	**±SE**	**Median**	**±SE**
Negative	18.000	±0.800	11.000	±0.67
Positive	23.630	±1.450	23. 00	±0.97
Log Rank	4.77		55.80	
***P*-value**	0.029*		0.000*	

*=significant

Table 8. EFS in relation to CD 45, CD 56

	CD 45		*CD56*	
	Median	***±SE***	***Median***	***±SE***
Negative	*18.000*	*±1.23*	*11.000*	*±0.670*
Positive	*23.630*	*±0.98*	*22*	*±0.75*
Log Rank	*5.27*		*55.800*	
P-value	*0.0215*		*0.001**	

*=significant

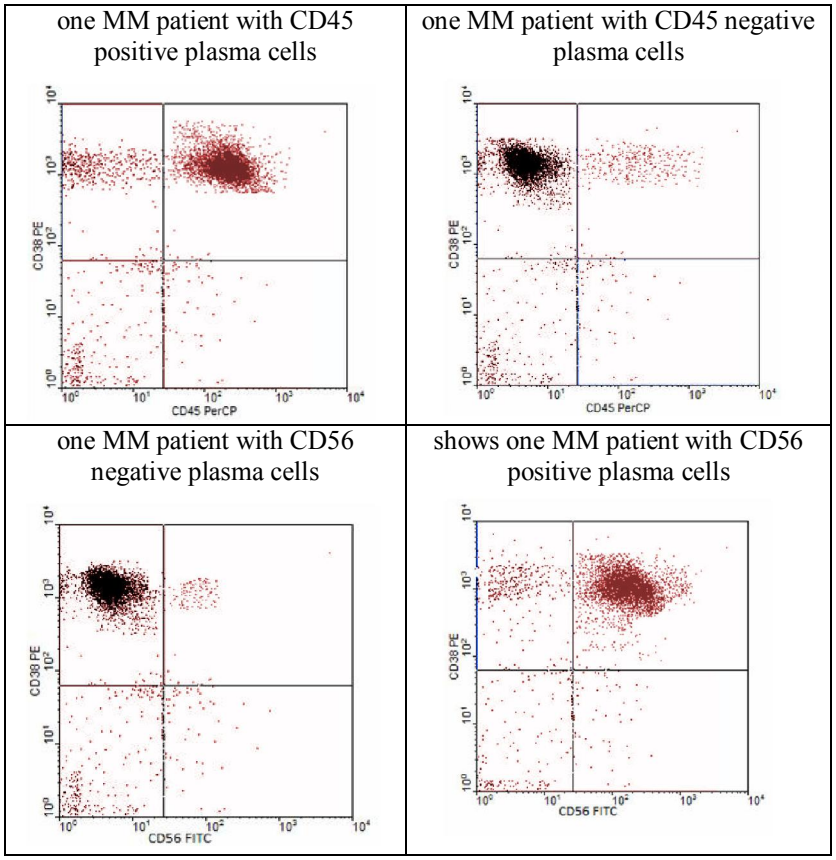

Figure 1. Flowcytomety images

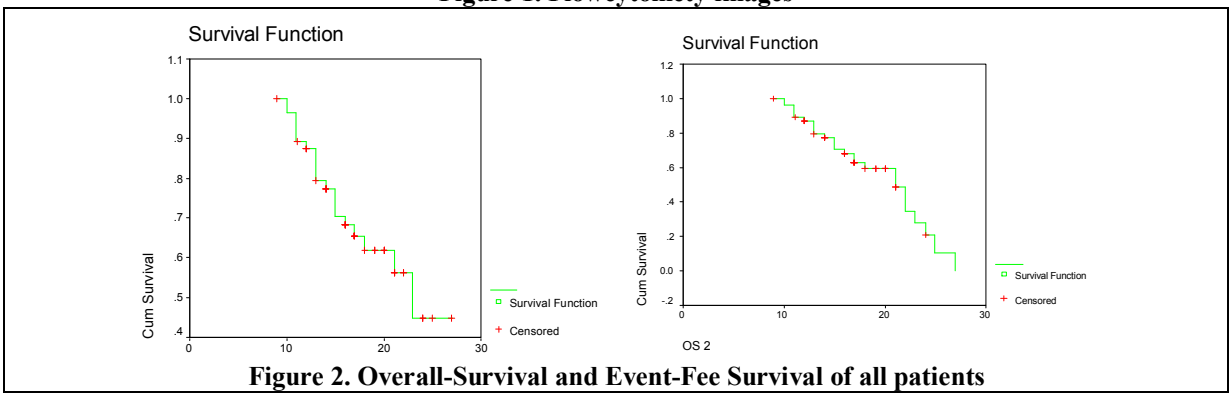

Figure 2. Overall-Survival and Event-Fee Survival of all patients

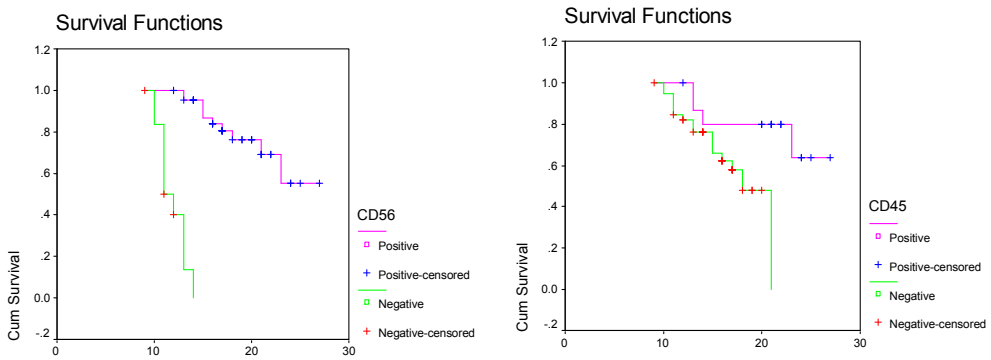

Figure 3. Overall-Survival according to CD 45 and CD 56

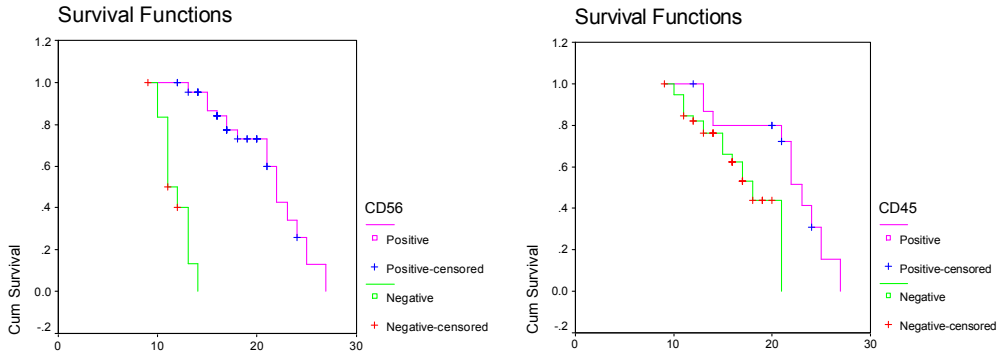

Figure 4. Event-Fee Survival of patients according to CD 45 and CD 56

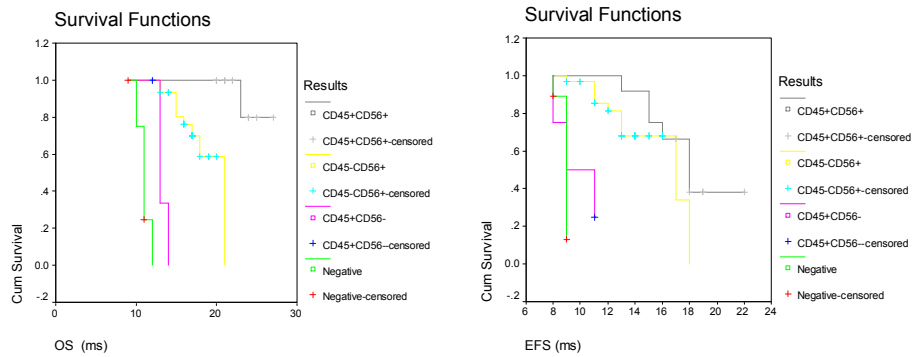

Figure 5. Overall-Survival and Event-Free Survival of patients either both markers –ve or both +ve

4. Discussion

In our study, 19 patients (34%) with previously untreated myeloma showed CR to VAD treatment, 35 patients (62.5%) showed PR and 2 patients (3.5%) showed SD. Anderson *et al.* [15] treated seventy-five newly diagnosed myeloma patients with VAD and demonstrated CR in 27% while 63% showed PR. Also, chim *et al.* [16] showed that 11 cases out of 25 (44%) exposed to VAD responded to treatment defined as ≥75% reduction in paraprotein while 14 patients (56%) showed <75% reduction in paraprotein, and were changed to another line of treatment.

The percentage of CD45 –ve patients in our study was 71%. Those patients who lack of CD45 expression had significantly elevated lytic bone lesions (P=0.01) whereas no significant changes were detected in β_2- microglobulin, creatinine, Hgb%, LDH and ISS. In agreement with our results Kumar *et al.* [17] showed that among the 46 patients with advanced

disease, there was strong correlation between presence of lytic bone lesions on skeletal survey and percentage of plasma cells expressing CD45 with the mean percentage of CD45 plasma cells was 14% for those with bone lesions compared to 34% for those with none; *P*=0.02. Besides, they showed that the proportion of plasma cells expressing CD45 is higher among those with early disease monoclonal gammaopathy of undetermined significance or smoldering MM compared to those with advanced disease (new or relapsed MM).

We found that patients who lack the CD45 expression on their cells had significantly shorter survival than patients without CD45expression. Among CD45+ve cases, 12 patients achieved CR versus 7 CD 45–ve patients while PR was achieved in 4 CD 45 +ve patients versus 31 in CD 45-ve patients (*P*=0.001). Also, median OS in CD45-ve patients was significantly less compared to CD 45+ve patient (median 18 versus 23 months, *P*=0.029). In addition, CD45-ve patients had significantly less median EFS compared to CD 45+ve patient (median 18 versus 23 months *P* = 0.021). In agreement with our results, Moreau et al [4] suggested that the CD 45–ve phenotype could reflect the phenotype of progressive disease in relation to the intrinsic malignancy of the MM clone and hence lacking CD45 expression at diagnosis had a significantly worse median OS than those retaining CD45 expression in their study. This could be attributed to less sensitivity of CD 45–ve myeloma cells to apoptosis and their greater capacity to circulate, disseminate and clone, and thus a greater malignancy [4, 18].

Similar to other studies [19-21] we showed that the percentage of CD56 expression was 77%. This was associated with significantly higher ISS and multiple lytic bone lesions. On the other hand, lack of CD56 expression was associated with significant elevation in β_2 microglubinemia, creatinine, Hgb%, LDH. Sahara *et al.* [7] analyzed CD56 expression in 70 patients with MM to determine its clinicopathological and prognostic significance. In their study, 21% patients were CD56-ve and had higher β_2 microglobulin levels with higher incidence of extramedullary disease, Bence Jones protein, renal insufficiency and thrombocytopenia than CD56+ patients. They attributed the higher incidence of plasmablastic cases to the possible development of CD56– MM from a less mature plasma cell than CD56+ MM.

Nineteen patients got CR in CD56+ve cases compared to 0 case in CD56-ve whereas PR was seen in 12 CD56-ve patients versus 23 patients in CD 56 +ve. Also, median OS in CD56-ve patients was significantly less compared to CD 56+ve patient (median 11 versus 23 months *p*- value 0.000). Sahara *et al.* [7] investigated MM patients treated with conventional chemotherapy by flowcytometry and showed that 15 out of 70 were CD56-ve and had a significantly shorter median OS than CD56+ve. On the other hand, Mathew *et al.* [22] reported that lack of CD56 expression was not related to a poor prognostic factor. Moreover, Chang *et al.* [9],by immunohistochemistry of bone marrow, studied107 patients with MM and demonstrated that CD56-ve patients (n=31) did not confer a poor prognosis. This discrepancy may be due to that high-dose therapy and autologous stem cell transplant might overcome adverse impact of CD56-ve expression on patients treated with conventional chemotherapy alone.

We used VAD as a first line therapy for MM patients since it is the routine practice in our institute as it is cost-effective while other frontline expensive therapies would be affordable only to non responders. Although VAD was introduced long time ago, recently, Chim *et al.* [16] compared VAD treatment with PAD (bortezomib, doxorubicin, dexamethasone) or VTD (bortezomib, thalidomide, dexamethasone) as induction therapy where they showed that 44%(11/25 patients) receiving the VAD treatment achieving ≥75% reduction in paraprotein after only three cycles of VAD.

The median OS and EFS for MM patients when both markers are expressed together is significantly longer compared to when both are simultaneously absent (*P*=0.000). Further studies are needed to find out whether a more aggressive course would be anticipated if both markers are not expressed rather than one marker

In conclusion, simultaneously analyzed CD56 or CD45 on bone marrow plasma cells from non transplant eligible MM patients can lend a hand to identify patients at high risk of grave disease progression. More aggressive therapy is thus might be recommended as a first line therapy in those patients who lack the aforementioned CD expressions.

Corresponding Author:
Nashwa Mohammad Noreldin M.D.,
Associate Professor, Internal Medicine Department
Head of Hematology Unit, Tanta Hospital of the University, Egypt
Email: nashwanor@hotmail.com

References

1. Pellat-Deceunynck C, Bataille R. Normal and malignant human plasma cells: proliferation, differentiation, and expansions in relation to CD45 expression. Blood Cells Mol Dis 2004; 32: 293–301.
2. Asosingh K, De Raeve H, Van Riet I, Van Camp B, Vanderkerken K. Multiple myeloma tumor

progression in the 5T2MM murine model is a multistage and dynamic process of differentiation, proliferation, invasion, and apoptosis. Blood 2003; 101:3136–41.
3. Drach J, Gattringer C, Huber H. Expression of the neural cell adhesion molecule (CD56) by human myeloma cells. Clin Exp Immunol 1991;83:418–22.
4. Moreau P, Robillard N, Avet-Loiseau H, *et al.* Patients with CD45 negative MM receiving high-dose therapy have a shorter survival than those with CD45 positive MM. Haematologica 2004; 89:547-51.
5. Van Camp B, Durie BGM, Spier C, de Waele M, van Riet I, Vela E, et al. Plasma cells in multiple myeloma express a natural killer cell-associated antigen: CD56 (NKH-1; Leu- 19). Blood 1990;76:377–86.
6. Ely SA, Knowles DM. Expression of CD56/neural cell adhesion molecule correlates with the presence of lytic bone lesions in multiple myeloma and distinguishes myeloma from monoclonal gammopathy of undetermined significance and lymphomas with plasmacytoid differentiation. Am J Pathol 2002;160:1293–99.
7. Sahara N, Takeshita A, Shigeno K, *et al.* Clinicopathological and prognostic characteristics of CD56-negative MM. Br J Haematol 2002;117:882-5.
8. Kraj M, Sokołowska U, Kopeć-Szlęzak J *et al.* Clinicopathological correlates of plasma cells CD56 (NCAM) expression in multiple myeloma. Leuk Lymphoma. 2008;49:298–305.
9. Chang H, Samiee S, Yi QL. Prognostic relevance of CD56 expression in MM: A study including 107 cases treated with high-dose melphalan-based chemotherapy and autologous stem cell transplant. Leuk Lymphoma 2006;47:43-7.
10. Greipp PR, San Miguel J, Durie BGM, *et al.* ISS for MM. J Clin Oncol 2005; 23: 3412–3420.
11. Mineur P, Menard JF, Le Loet X, *et al.* VAD or VMBCP in MM refractory to or relapsing after cyclophosphamide-prednisone therapy (protocol MY 85). Br J Haematol 1998;103:512–517.
12. Durie BG, Harousseau JL, Miguel JS *et al.* International uniform response criteria for multiple myeloma. Leukemia 2006; 20: 1467–1473.
13. Weber DM, Rankin K, Gavino M, *et al.*: Thalidomid alone or with dexamethasone for previously untreated multiple myeloma. J Clin Oncol 21:16-19, 2003
14. National Cancer Institute at the national Institute of health. Available at http://www.cancer.gov/dictionary?CdrID= (44070 and 655269)
15. Anderson H, Scarffe JH, Ranson M, *et al.* VAD chemotherapy as remission induction for MM. Br J Cancer. 1995;71:326–330.
16. Chim CS, Lie AKW , Chan EYT *et al.* Treatment outcome and prognostic factor analysis in transplant-eligible Chinese myeloma patients receiving bortezomib-based induction regimens including the staged approach, PAD or VTD. Journal of
17. Kumar S, Rajkumar S, Kimlinger T, *et al.* CD45 expression by bone marrow plasma cells in MM: clinical and biological correlations. Leukemia 2005;19:1466-70.
18. Kawano MM, Ishikawa H, Tsuyama, N, Abron S, Liu S, Li FJ, *et al.* Growth mechanism of human myeloma cells by interleukin- 6. Int J Hematol 2002; 76 Suppl1: 329-33.
19. Pellat-Deceunynck C, Barille S, Jego G *et al.* The absence of CD56 (NCAM) on malignant plasma cells is a hallmark of plasma cell leukemia and of a special subset of multiple myeloma. Leukemia. 1998;12:1977–1982.
20. Mateo G, Montalban MA, Vidriales MB, *et al.* Prognostic value of immunophenotyping in MM: a study by the PETHEMA/GEM cooperative study groups on patients uniformly treated with high-dose therapy. J Clin Oncol. 2008;26:2737-44.
21. Raswstron A, Barrans S, Blythe D, *et al.* Distribution of myeloma plasma cells in peripheral blood and bone marrow correlates with CD56 expression. Br J Haematol 1999;104:138–43.
22. Mathew, P., Ahmann, G.J., Witzig, T.E., Roche, P.C., Kyle, R.A. &Greipp, P.R. () Clinicopathological correlates of CD56 expression in MM: a unique entity? Br J Haematol, 1995;90:459–61.

10/22/2013