MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2017; 23: 2636-2643
DOI: 10.12659/MSM.901850

Received: 2016.10.07
Accepted: 2016.11.16
Published: 2017.05.30

High Expression of Phosphorylated Extracellular Signal-Regulated Kinase (ERK1/2) is Associated with Poor Prognosis in Newly Diagnosed Patients with Multiple Myeloma

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 Liping Fan
CF 2 Jinquan Hong
ABCDEFG 1 Haobo Huang
ACDE 1,3 Danhui Fu
BCF 3 Shunquan Wu
BC 3 Qingqing Wang
BC 3 Yamei Ye
B 3 Yun Liu

1 Department of Blood Transfusion, Fujian Medical University Union Hospital, Fuzhou, Fujian, P.R. China
2 Department of Anesthesia, The Second Affiliated Hospital of Fujian Medical University, Quanzhou, Fujian, P.R. China
3 Department of Hematology, Fujian Medical University Union Hospital and Fujian Institute of Hematology, Fuzhou, Fujian, P.R. China

Corresponding Authors: Haobo Huang, e-mail: huanghaobo1981@163.com, Danhui Fu, e-mail: fudanhui@189.cn

Source of support: The present study was funded by the Joint Funds for the innovation of science and Technology of Fujian province (Fuzhou, China; Grant no. 2016Y9027), the Natural Science Foundation of Fujian Province (Fuzhou, China;Grant no. 2016J01461), the Medical Elite Cultivation Program of Fujian Province (Fuzhou, China; Grant no. 2015-ZQN-JC-18), and the Middle-Aged and Young Teacher Education and Research Program of Fujian Province (Fuzhou, China; Grant no. JA14133)

Background: Previous research has demonstrated that the extracellular signal-regulated kinase (MEK)/extracellular signal-regulated kinase (ERK) signaling pathway is commonly activated in multiple myeloma (MM) patients. However, the prognostic value of activation of the MEK/ERK signaling pathway in newly diagnosed patients with MM has not been reported.

Material/Methods: Expression levels of p-ERK1/2 protein in bone marrow biopsy specimens obtained from 60 newly diagnosed patients with MM were analyzed using immunohistochemistry, and classified into 3 groups: high p-ERK1/2 expression, low p-ERK1/2 expression, and negative group. Correlations between clinicopathological characteristics, including expression levels of p-ERK1/2 protein, progression-free survival (PFS), and overall survival (OS), were analyzed using univariate and multivariate analysis.

Results: Phosphorylated-ERK1/2 protein was positive in 47 bone marrow specimens, including 19 specimens with high p-ERK1/2 expression and 28 specimens with low p-ERK1/2 expression. Univariate Kaplan-Meier analysis showed that in newly diagnosed patients with MM, high p-ERK1/2 expression, high ISS staging, serum creatinine (Scr) ≥177 μmol/l, serum β_2-microglobulin (β_2-MG) ≥5.5 μmol/l, and serum calcium (Ca) ≥2.75 mmol/l were significantly associated with shorter OS and PFS. Additionally, high ECOG scores (score 2–4) were associated with shorter PFS in newly diagnosed patients with MM. Multivariate Cox regression analysis showed that in newly diagnosed patients with MM, high p-ERK1/2 expression was significantly associated with shorter OS and PFS. Additionally, in newly diagnosed patients with MM, serum Ca ≥2.75 mmol/l was significantly associated with shorter PFS, and serum β_2-MG ≥5.5 μmol/l was significantly associated with shorter OS.

Conclusions: High p-ERK1/2 expression is an independent factor for poor prognosis in newly diagnosed patients with MM.

MeSH Keywords: Biopsy • Bone Marrow • MAP Kinase Signaling System • Multiple Myeloma • Prognosis

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/901850

1895 3 2 25

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Background

Multiple myeloma (MM) is a malignant plasma cell disease, characterized by the clonal proliferation of plasma cells in bone marrow, accounting for 10-15% of all hematological malignancies. Some Chinese experts predicted that there are about 200 000 cases in China [1]. Several studies revealed that clinical outcome of patients is heterogeneous, and the pathogenesis of MM is not understood clearly [2,3]. Therefore, exploration of pathogenic development of MM may help to improve MM patient outcome.

The extracellular signal-regulated kinase (MEK)/extracellular signal-regulated kinase (ERK) signaling transduction pathway can be activated in response to extracellular stimuli, and has been reported to play an important role in several pathophysiological processes such as cell proliferation and cell death. After stimulation, ERK1/2 protein of the MEK/ERK signaling pathway is phosphorylated, leading to activation of downstream targets [4–6]. Recent studies found that abnormal activation of the MEK/ERK signaling pathway is involved in pathogenesis of many kinds of solid tumors and hematological malignancies, including MM [7–14]. Furthermore, the MEK/ERK signaling pathway participates in abnormal biological behavior of MM cells, induced by some intracellular or extracellular stimuli [15,16]. In MM, abnormality of the MEK/ERK signaling pathway is recurrent and is detected only on the genomic level, not on the protein level [13]. Furthermore, the correlation between ERK signaling pathway abnormality and survival time in MM patients has not been reported.

In this study, we detected the expression of phosphorylated-ERK1/2 (p-ERK1/2) protein in 60 bone marrow biopsy specimens obtained from newly diagnosed patients with MM. We analyzed the correlations among expression levels of p-ERK1/2 protein, clinicopathological characteristics, and survival data of these patients, aiming to gain insight into the potential role of the ERK1/2 signaling pathway in pathogenesis of MM and its prognosis value in newly diagnosed patients with MM.

Material and Methods

Patients and samples

A total of 60 formalin-fixed, paraffin-embedded bone marrow biopsy specimens were obtained from newly diagnosed patients with MM at Fujian Medical University Union Hospital (Fuzhou, China) from January 2012 to February 2015. Before bone marrow biopsy, no prior chemotherapy was administered in any case. This study was approved by the Ethics Committee of Fujian Medical University Union Hospital. The samples were collected with patient consent.

Immunohistochemistry and evaluation of p-ERK1/2 protein expression

The thickness of the sections was 5 μm. Antigen retrieval was carried out in 10 mmol/l sodium citrate buffer (pH 6.0) at 120°C for 5 min in a pressure cooker. Endogenous peroxidase activity was blocked with 3% H_2O_2 at 37°C for 10 min. Sections were incubated with p-ERK1/2 rabbit monoclonal antibody (CST-4370, dilution 1: 400) (Cell Signaling Technologies, USA) at 37°C for 60 min. Immunoreactive proteins were visualized with the MaxVision™ HRP-Polymer Anti-Rabbit IHC Kit (Maixin Bio, China) following the manufacturer's protocol. Negative control sections were treated without p-ERK1/2 antibody under the same experimental conditions. Lastly, sections were counterstained with hematoxylin and observed by microscopy (BX41 microscope, Olympus Corporation, Tokyo, Japan) in a number of high-power microscopic fields (magnification, ×400).

Evaluation of p-ERK1/2 protein expression was performed by 2 pathologists blinded to the clinicopathological and survival information of the patients, according to the intensity of cellular staining and the percentage of positively immunoreactive cells. If disagreement emerged regarding the same slide, the pathologists discussed it until a consensus score was achieved. The p-ERK1/2 protein was immunohistochemically stained yellow-brown in the cytoplasm and/or nuclei of plasma cells. The staining intensity was scored as [17]: no staining, score 0; weak staining, score 1; moderate staining, score 2; and strong staining, score 3. The proportion of stained plasma cell was scored as: ≤5% positive cells, score 0; 6–25% positive cells, score 1; 26–50% positive cells, score 2; 51–75% positive cells, score 3; and ≥75% positive cells, score 4. The expression level of p-ERK1/2 protein was considered negative if the total score (intensity score and positive cells score) was 0, low if it was 1 or 2, and high if it was 3 or more.

Statistical analysis

Clinical event end-points were evaluated by use of the International Myeloma Working Group criteria. Overall survival (OS) was measured from the date of diagnosis to the date of death or last follow-up. Death from all causes was included. Progression-free survival (PFS) was measured from the date of treatment start to the date of disease progression, relapse, or death, whichever came first. Survival time was measured until 31 December 2015.

The χ^2 test (categorical variables) and Student's t-test (continuous variables) were used to analyze the correlation between expression levels of p-ERK1/2 protein and demographic and clinicopathological characteristics of newly diagnosed patients with MM. Kaplan-Meier method was used to plot the survival curves. The log-rank test was used to analyze the differences

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Table 1. Demographic and clinicopathological characteristics of primary MM patients.

Demographic and clinicopathological characteristics		Total	p-ERK1/2 expression (group)			P-value
			High (A)	Low (B)	Negative (C)	
Age (years)			63.21±2.84	55.96±2.16	56.77±3.38	0.11
Sex	Male	36	14	13	9	0.13
	Female	24	5	15	4	
Ig isotype	IgG	29	10	15	4	0.51
	IgA	20	7	7	6	
	Light chain	11	2	6	3	
ISS staging	I	12	1	6	5	0.04
	II	25	6	14	5	
	III	23	12	8	3	
ECOG scoring	0–1	48	13	24	11	0.42
	2–4	12	6	4	2	
Plt (×10^9/L)	≥100	50	15	23	12	0.59
	<100	10	4	5	1	
Hb (g/L)	≥100	19	4	10	5	0.48
	<100	41	15	18	8	
Scr (μmol/L)	≥177	7	4	1	2	0.17
	<117	53	15	27	11	
Serum Alb (g/L)	≥35	16	2	7	7	0.02
	<35	44	17	21	6	
Serum β_2-MG (μmol/L)	≥5.5	19	11	5	3	0.01
	<5.5	41	8	23	10	
Serum LDH (IU/L)	≥245	12	5	6	1	0.42
	<245	48	14	22	12	
Serum Ca (mmol/L)	≥2.75	7	4	2	1	0.30
	<2.75	53	15	26	12	
Bortezomib	Yes	27	10	11	6	0.66
	No	33	9	17	7	
Thalidomide	Yes	35	13	14	8	0.44
	No	25	6	14	5	
Auto-HSCT	Yes	10	1	5	4	0.16
	No	50	18	23	9	

Ig – immunoglobulin; ISS – International Staging System; ECOG – Eastern Cooperative Oncology Group; Plt – platelet; Hb – hemoglobin; Scr – serum creatinine; Alb – albumin; β_2MG – β_2-microglobulin; LDH – lactate dehydrogenase; Ca – calcium; Auto-HSCT – autologous hematopoietic stem cell transplantation.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

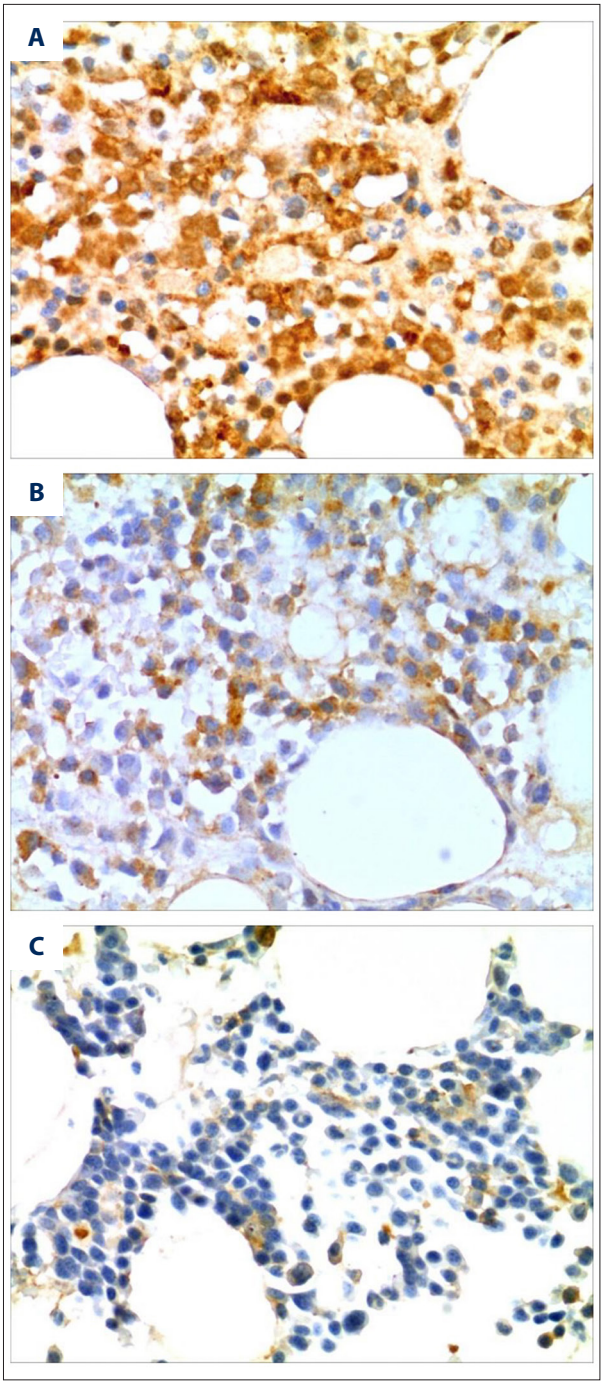

Figure 1. Immunohistochemical staining of p-ERK1/2 in bone marrow biopsy specimens of MM patients (magnification, ×400). Different expression levels of p-ERK1/2 protein were found in these specimens: (**A**) high expression, (**B**) low expression, and (**C**) negative.

in these survival curves. The Cox regression model was used for multivariate analysis, with adjustments for characteristics that might be significant prognostic factors according to the univariate analysis. P<0.05 was used as the criterion for statistical significance. SPSS19.0 software was used for statistical analysis.

Results

Demographic and clinicopathological characteristics of MM patients

The demographic and clinicopathological characteristics of 60 newly diagnosed patients with MM are summarized in Table 1. Ages of these patients ranged from 35 to 81. After bone marrow biopsy, all patients were treated with at least 2 courses of chemotherapy regimens containing bortezomib and/or thalidomide, and/or autologous hematopoietic stem cell transplantation. The median follow-up of all patients was 16.1 (0.3–48) months. During the follow-up period, 21 deaths occurred.

Expression of p-ERK1/2 in bone marrow biopsy specimens and its correlation with demographic and clinicopathological characteristics of MM patients

The immunohistochemistry (IHC) results showed that expression of p-ERK1/2 protein was positive in 47 of 60 bone marrow specimens. According to evaluation criterion of p-ERK1/2 protein expression, 60 newly diagnosed patients with MM were classified into 3 groups: 19 patients with high p-ERK1/2 expression (group A), 28 patients with low p-ERK1/2 expression (group B), and 13 patients without p-ERK1/2 expression (group C) (Figure 1, Table 1).

The demographic and clinicopathological characteristics according to expression levels of p-ERK1/2 protein are listed in Table 1. There were significant differences in 3 characteristics – ISS staging, serum albumin (Alb) level, and serum β_2-MG level – among patients in these 3 groups. However, there were no significant differences in other characteristics such as age, sex, ECOG scoring, immunoglobulin (Ig) isotype, hemoglobin (Hb) level, platelet (Plt) counts, serum creatinine (Scr) level, serum lactate dehydrogenase (LDH) level, serum calcium (Ca) level, and therapeutic regimens containing bortezomib, thalidomide, and/or autologous hematopoietic stem cell transplantation (auto-HSCT) among patients in these 3 groups (Table 1).

Correlation between expression of p-ERK1/2 protein and survival time in newly diagnosed patients with MM

To elucidate the relationship between expression levels of p-ERK1/2 protein and survival time in newly diagnosed patients with MM, univariate Kaplan-Meier and multivariate Cox regression analysis were performed.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Table 2. Univariate analysis of the correlation between demographic and clinicopathological characteristics and survival time in primary MM patients.

Demographic and clinicopathological characteristics		Overall survival time (mean, month)	Log-rank test	P	Progression-free survival time (mean, month)	Log-rank test	P
Age	≥60	15.712	1.733	0.188	14.786	0.072	0.788
	<60	19.165			15.836		
Sex	Male	16.260	1.134	0.287	14.082	1.401	0.237
	Female	19.637			17.286		
Ig isotype	IgG	17.347	0.070	0.966	14.686	0.059	0.809
	IgA	17.650			14.915		
	Light chain	18.235			17.966		
ISS staging	I	22.182	6.094	0.048	21.653	5.085	0.024
	II	19.166			14.766		
	III	13.535			12.732		
ECOG	0–1	18.206	0.989	0.320	16.251	4.148	0.042
	2–4	15.230			11.816		
Plt (×10^9/L)	≥100	17.250	1.111	0.292	15.286	0.190	0.663
	<100	19.413			15.753		
Hb (g/L)	≥100	21.189	1.678	0.195	18.657	2.705	0.100
	<100	15.953			13.838		
Scr (μmol/L)	≥177	10.110	7.047	0.008	9.396	5.169	0.023
	<177	18.602			16.152		
Serum Alb (g/L)	≥35	17.855	**<0.001**	0.989	17.469	0.963	0.327
	<35	17.522			14.598		
Serum β_2-MG (μmol/L)	≥5.5	11.416	13.173	**<0.001**	10.623	7.908	0.005
	<5.5	20.482			17.561		
Serum LDH (IU/L)	≥245	16.997	0.022	0.883	14.266	0.140	0.709
	<245	17.764			15.638		
Serum Ca (mmol/L)	≥2.75	8.781	15.119	**<0.001**	7.372	22.136	**<0.001**
	<2.75	18.777			16.419		
Bortezomib	Yes	17.371	0.020	0.887	15.159	0.001	0.979
	No	17.820			15.543		
Thalidomide	Yes	16.798	1.271	0.260	14.934	0.383	0.536
	No	18.749			15.965		
Auto-HSCT	Yes	19.983	0.491	0.483	17.020	0.171	0.679
	No	17.136			15.032		
p-ERK1/2 expression	High (A)	9.792	23.674	**<0.001**	8.604	8.673	0.003
	Low (B)	22.010			19.028		
	Negative (C)	19.564			17.352		

Ig – immunoglobulin; ISS – International Staging System; ECOG – Eastern Cooperative Oncology Group; Plt – platelet; Hb – hemoglobin; Scr – serum creatinine; Alb – albumin; β_2-MG – β_2-microglobulin; LDH – lactate dehydrogenase; Ca – calcium; Auto – HSCT-autologous hematopoietic stem cell transplantation.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

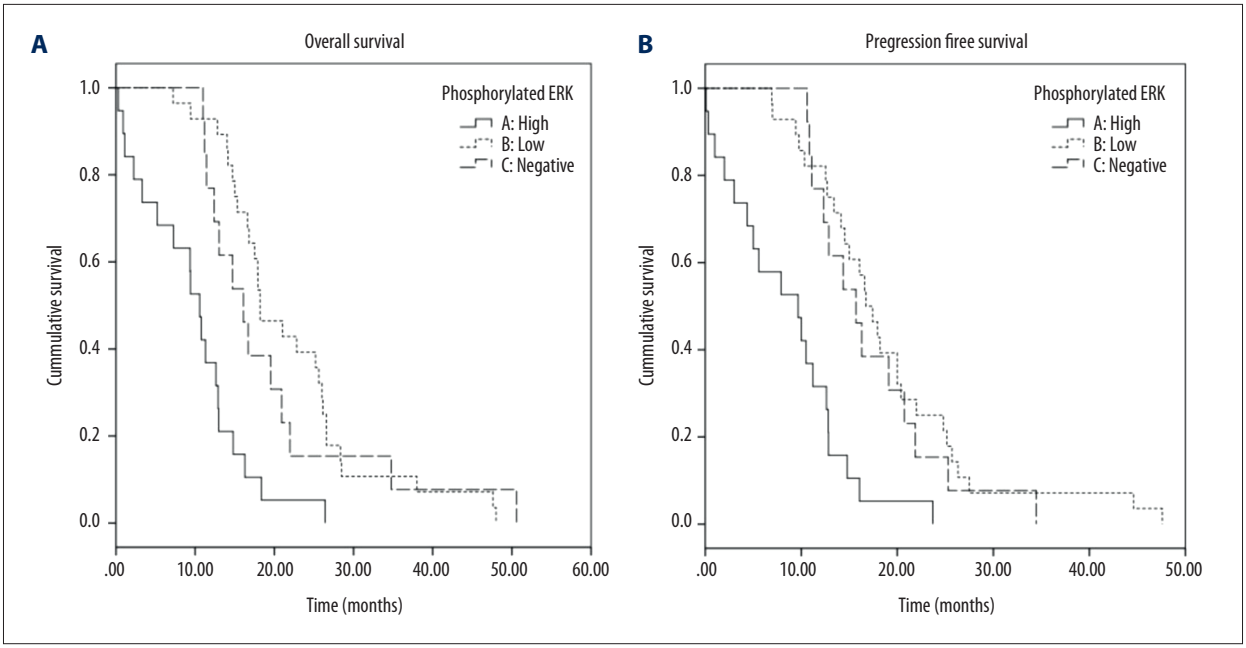

Figure 2. Kaplan-Meier survival curves of patients with newly diagnosed MM classified according to expression levels of p-ERK1/2 protein. (**A**) Overall survival. i. P=0.000, compared A with B; ii. P=0.007, compared A with C; iii. P=0.541, compared B with C. (**B**) Progression-free survival. i. P=0.000, compared A with B; ii. P=0.007, compared A with C; iii. P=0.496, compared B with C.

Table 3. Multivariate analysis of the correlation between clinicopathological characteristics and survival time in primary MM patients.

Covariates	Overall survival					Progression-free survival				
	Coefficient	Standard error	HR	95%CI for HR	P	Coefficient	Standard error	HR	95%CI for HR	P
ISS staging	–0.097	0.257	0.907	0.548–1.502	0.705	0.044	0.237	1.045	0.656–1.664	0.853
Scr (μmol/L)	0.019	0.640	1.019	0.290–3.574	0.977	–0.100	0.587	0.905	0.287–2.857	0.865
β_2-MG (μmol/L)	0.928	0.470	2.530	1.006–6.358	0.048	0.432	0.436	1.541	0.656–3.618	0.321
Ca (mmol/L)	1.010	0.619	2.745	0.816–9.231	0.103	1.715	0.605	5.559	1.697–18.212	0.005
p-ERK1/2 expression	–0.575	0.234	0.563	0.355–0.891	0.014	–0.546	0.226	0.579	0.372–0.901	0.015
ECOG	N.A.	N.A.	N.A.	N.A.	N.A.	0.544	0.348	1.722	0.870–3.407	0.118

ISS – International Staging System; ECOG – Eastern Cooperative Oncology Group; Scr – serum creatinine; Alb – albumin; β_2-MG – β_2-microglobulin; Ca – calcium; HR – hazard ratio; CI – confidence interval; N.A. – not available.

Univariate analysis showed that in MM patients, expression level of p-ERK1/2 protein was negatively associated with OS and PFS. The OS and PFS of patients in group A were shorter than those in group B and group C. Furthermore, there were no significant differences in OS and PFS between patients in group B and those in group C (Figure 2, Table 2). In addition, the shorter OS in newly diagnosed patients with MM was significantly associated with high ISS staging, Scr ≥177 μmol/l, serum β_2-MG ≥5.5 μmol/l, and serum Ca ≥2.75 mmol/l, and the shorter PFS was significantly associated with high ISS staging, high ECOG scoring, Scr ≥177 μmol/l, serum β_2-MG ≥5.5 μmol/l, and serum Ca ≥2.75 mmol/l (Table 2).

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Multivariate analysis showed that in MM patients, high expression level of p-ERK1/2 protein was significantly associated with OS and PFS. Additionally, serum Ca ≥2.75 mmol/l was significantly associated with PFS, and serum β_2-MG ≥5.5 μmol/l was significantly associated with OS (Table 3).

Discussion

MM is an incurable malignant plasma cell disease. A growing number of studies show that pathogenesis and clinical outcome of MM patients are highly heterogeneous [1,18–21]. Recent studies using gene expression profiling show that the MEK/ERK signaling pathway is abnormally activated in over 50% of MM patients [13]. MEK/ERK signaling pathway inhibitor can show cytotoxicity on MM cells from newly diagnosed patients and MM cell lines *in vitro* [22,23]. Furthermore, MEK inhibitor used alone or in combination with conventional chemotherapy showed weak or moderate cytotoxicity to MM cells *in vivo*, leading to partial remission in some refractory/relapse patients with MM in a clinical trial. Some clinical trials are ongoing to evaluated the efficacy of new MEK inhibitor on patients with MM [23]. The above evidence indicates that inhibition of the MEK/ERK signaling pathway may be a useful strategy for MM treatment. However, there has been no published research on the effect of activated molecules in the MEK/ERK signaling pathway, such as p-ERK1/2, on protein level, and the correlation between p-ERK1/2 protein expression and survival time in newly diagnosed patients with MM has been not reported.

The present study shows that the positive rate of p-ERK1/2 in bone marrow biopsy specimens of newly diagnosed patients with MM is high (78.3%), in agreement with a previous study showing that activation of the ERK signaling pathway is common in myeloma [13]. We then classified 60 patients into 3 groups according to expression levels of p-ERK1/2 protein, showing that expression levels of p-ERK1/2 were positively associated with ISS staging, serum albumin level, and serum β_2-MG level in these patients. However, there were not significant differences in the other clinicopathological characteristics mentioned above among patients in these 3 groups.

Before analysis of the correlation between expression levels of p-ERK1/2 protein and survival time in newly diagnosed patients with MM, in these 3 groups we analyzed the therapeutic regimens that have been considered to benefit MM patient survival time [24,25]. We also found that there was no significant difference in therapeutic regimens containing bortezomib and thalidomide, and auto-hematopoietic stem cell transplantation among patients in these 3 groups.

Subsequently, in univariate analysis, we found that expression levels of p-ERK1/2 protein, high ISS staging, serum Cr ≥177 μmol/l, serum β_2-MG ≥5.5 μmol/l, and serum Ca ≥2.75 mmol/l were poor prognostic factor for PFS and OS of newly diagnosed patients with MM. Otherwise, high ECOG scoring was a poor prognostic factor for PFS, but not for OS, of newly diagnosed patients with MM.

In multivariate analysis, we found that in newly diagnosed patients with MM, high expression level of p-ERK1/2 protein, but not low expression level of p-ERK1/2 protein, was an independent poor prognostic factor for OS and PFS of newly diagnosed patients with MM. In addition, in newly diagnosed patients with MM, serum Ca ≥2.75 mmol/l was also an independent poor prognostic factor for PFS, while serum β_2-MG ≥5.5 μmol/l was also an independent poor prognostic factor for OS.

Although ISS staging, consisting of serum albumin level and serum β_2-MG level, has been reported to be the most important prognostic system for MM [21], we found that it had no useful prognostic value. We found differences in ISS staging, serum albumin level, and serum β_2-MG level in newly diagnosed patients with MM with different expression levels of p-ERK1/2 protein, and these differences might have attenuated the prognostic function of ISS staging in our study.

Conclusions

Our data suggest that high expression of p-ERK1/2 protein is an independent factor for poor survival in newly diagnosed patients with MM, and therapeutic regimens targeting ERK1/2 may be of benefit to MM patients.

Conflicts of interest

None.

References:

1. Lu J, Lu J, Chen W et al: Clinical features and treatment outcome in newly diagnosed Chinese patients with multiple myeloma: results of a multicenter analysis. Blood Cancer J, 2014; 4: e239
2. Bergsagel PL, Kuehl WM: Molecular pathogenesis and a consequent classification of multiple myeloma. J Clin Oncol, 2005; 23(26): 6333–38
3. Fonseca R, Bergsagel PL, Drach J et al: International Myeloma Working Group molecular classification of multiple myeloma: spotlight review. Leukemia, 2009; 23(12): 2210–21
4. Ashford AL, Dunkley TP, Cockerill M et al: Identification of DYRK1B as a substrate of ERK1/2 and characterisation of the kinase activity of DYRK1B mutants from cancer and metabolic syndrome. Cell Mol Life Sci, 2016; 73(4): 883–900
5. Hu Y, Mintz A, Shah SR, Quinones-Hinojosa A, Hsu W: The FGFR/MEK/ERK/brachyury pathway is critical for chordoma cell growth and survival. Carcinogenesis, 2014; 35(7): 1491–99

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

6. Kabir ME, Singh H, Lu R et al: G Protein-coupled estrogen receptor 1 mediates acute estrogen-induced cardioprotection via MEK/ERK/GSK-3β pathway after ischemia/reperfusion. PLoS One, 2015; 10(9): e0135988
7. Chen Q, Lu HS, Gan MF et al: Expression and prognostic role of MEKK3 and pERK in patients with renal clear cell carcinoma. Asian Pac J Cancer Prev, 2015; 16(6): 2495–99
8. Ciccarelli C, Vulcano F, Milazzo L et al: Key role of MEK/ERK pathway in sustaining tumorigenicity and *in vitro* radioresistance of embryonal rhabdomyosarcoma stem-like cell population. Mol Cancer, 2016; 15: 16
9. Cui X, Li S, Li T et al: Significance of elevated ERK expression and its positive correlation with EGFR in Kazakh patients with esophageal squamous cell carcinoma. Int J Clin Exp Pathol, 2014; 7(5): 2382–91
10. Ding C, Luo J, Li L et al: Gab2 facilitates epithelial-to-mesenchymal transition via the MEK/ERK/MMP signaling in colorectal cancer. J Exp Clin Cancer Res, 2016; 35: 5
11. Hilton DA, Ristic N, Hanemann CO: Activation of ERK, AKT and JNK signaling pathways in human schwannomas *in situ*. Histopathology, 2009; 55(6): 744–49
12. Li XL, Chen XQ, Zhang MN et al: SOX9 was involved in TKIs resistance in renal cell carcinoma via Raf/MEK/ERK signaling pathway. Int J Clin Exp Pathol, 2015;8(4): 3871–81
13. Lionetti M, Barbieri M, Todoerti K et al: Molecular spectrum of BRAF, NRAS and KRAS gene mutations in plasma cell dyscrasias: Implication for MEK-ERK pathway activation. Oncotarget, 2015; 6(27): 24205–17
14. Wang D, Han S, Peng R et al: FAM83D activates the MEK/ERK signaling pathway and promotes cell proliferation in hepatocellular carcinoma. Biochem Biophys Res Commun, 2015; 458(2): 313–20
15. Ma Y, Jin Z, Huang J et al: IQGAP1 plays an important role in the cell proliferation of multiple myeloma via the MAP kinase (ERK) pathway. Oncol Rep, 2013; 30(6): 3032–38
16. Jin Y, Dai Z: USO1 promotes tumor progression via activating Erk pathway in multiple myeloma cells. Biomed Pharmacother, 2016; 78: 264–71
17. Sun YQ, Xie JW, Chen PC et al: Low expression of CDK5 and p27 are associated with poor prognosis in patients with gastric cancer. J Cancer, 2016; 7(9): 1049–56
18. Avet-Loiseau H, Fonseca R, Siegel D et al: Carfilzomib significantly improves the progression-free survival of high-risk patients in multiple myeloma. Blood, 2016; 128(9): 1174–80
19. Jian Y, Chen X, Zhou H et al: Prognostic impact of cytogenetic abnormalities in multiple myeloma: A retrospective analysis of 229 patients. Medicine (Baltimore), 2016; 95(19): e3521
20. Moreau P, Masszi T, Grzasko N et al: Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med, 2016; 374(17): 1621–34
21. Szabo AG, Gang AO, Pedersen MØ et al: Overexpression of c-myc is associated with adverse clinical features and worse overall survival in multiple myeloma. Leuk Lymphoma, 2016; 57(11): 2526–34
22. Suzuki R, Kikuchi S, Harada T et al: Combination of a selective HSP90α/β inhibitor and a RAS-RAF-MEK-ERK signaling pathway inhibitor triggers synergistic cytotoxicity in multiple myeloma cells. PLoS One, 2015; 10(12): e0143847
23. Chang-Yew Leow C, Gerondakis S, Spencer A. MEK inhibitors as a chemotherapeutic intervention in multiple myeloma. Blood Cancer J, 2013; 3: e105
24. Fujisawa M, Suehara Y, Fukumoto K et al: Changes in survival rate of multiple myeloma after the introduction of bortezomib: A single institutional experience over 20 years. Ann Hematol, 2016; 95(1): 63–72
25. Lu J, Lu J, Liu A, et al: The applicability of the international staging system in Chinese patients with multiple myeloma receiving bortezomib or thalidomide-based regimens as induction therapy: a multicenter analysis. Biomed Res Int, 2015; 2015: 856704

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]