Progression and Free Progression Survival Indices in Patients with Multiple Myeloma

Sadik A. Abdullah[1], Waseem F. Al-Tameemi[2], Ghassan A.A. Al-Shamma[2]

[1]Research Scholar, Departments of Chemistry, College of Medicine, Al-Nahrain University, Iraq,
[2]Research Scholar, Departments of Chemistry, College of Medicine, Al-Nahrain University.

Abstract

The main feature in multiple myeloma is osteolysis and, hence, bone turnover markers have got the at most care in different studies on this disease. The present paper would stress on the calculation of free progression survival indices using some of these markers .

Sixty-five MM (males=41, females=24) patients distributed to different hematologycenters in Iraq were enrolled in this study. Their age range was 39-81 years, they were distributed all on three stages of the diseaseaccording to the international staging system (ISS) : Group A – Stage I (n=21 patients, age mean 57.14±12.25 years), Group B – Stage II (n=22 patients, age mean of 56.45±11.33 years), and Group C-Stage III (n=22 patients, age mean 60.59±11.55 years). Blood samples were taken from each patient just prior to starting the chemotherapy for the measurement of blood hemoglobin (Hb), serum Creatinine, Calcium, β2 Microglubulin, Osteocalcin (OC), total and Beta C-terminal telopeptide (CTX, BCTX), Parathyroid hormone (PTH), Syndecan-1 (CD138), and both kappa & lambda free light chain (FLCκ, FLCλ).

There was no significant association between age, sex, body weight and residency with disease staging or progression. From the bone markers studied only CTX and BCTX were significantly associated with the disease progression and showing varying free progression patient survival times with CTX and BCTX at different concentrations.

The comparison between the results of the newly diagnosed and long-standing patients revealed that only total FLC, FLCκ, FLCλ and CD138 were significantly higher in the long-standing patients. Their sensitivity and specificity values were varying among these markers.

Keywords: *Progression, survival indices, multiple myeloma.*

Introduction

The annual incidence of multiple myeloma (MM) in the UK was reported to be 5/100 000, constituting about 10% of hematological malignancies and affecting middle sixties mostly with variation among different races and sex[(1)].

Corresponding Author,
Sadik A. Abdullaha
Research Scholar, Departments of Chemistry, College of Medicine , Al-Nahrain University, Iraq
e-mail: mustafasaleam@yahoo.com

It was reported that neither changes in monoclonal protein levels nor X-rays can be exact indices of the activity in bone turnover and thus, the need for biochemical markersfor bone activity in MM is essential[(2)].

Staging of MM, principally, depends on serum levels of β2-microglobulin and albumin (International staging system, ISS). The heterogenicity and variability of MM course led to the inclusion of other prognostic factors as C-reactive protein, lactate dehydrogenase, LDH, and cytogenetics by Fluorescence in situ hybridization, FISH[(3-4)].

Improvement in the survival of MM patients, in the last decade, including those with high risk has been

reported[5], Elevated C-reactive protein is considered a determinant predictor of lower survival rates in patients with several cancers incuding MM[6].

Classification of myeloma risk using the international staging system (ISS) and host factors such as age, performance status, and comorbidities are considered important for determining prognosis and choosing treatment options [7]. However, many parameters were suggested for these purposes, some concern demographic characteristics as age, residence, gender, race, or obesity [8-10], others are related to diagnostic results as radiology or laboratory findings as Hb, plasma cells, renal insufficiency, hypercalcemia, β2-microglobulin, free light chain, Parathyroid hormone, PTH, or immunofixation tests [11-17].

Bone markers have, also, been found to be related to MM staging in variable degrees as total and Beta C-Terminal telopeptide (CTX, BCTX), osteocalcin (OC), Syndecane-1 (CD138).(18,)with a statistically significant positive correlation between bone lesions degree and β-CTX levels[19].

Disease progression and free progression survival rates are two important tasks for treatment of patients with MM[20]. The present study elucidates and evaluates these two points for different biomarkersin a sample patient with MM.

Materials and Method

Hospital-Based cross-sectional research was conducted over eleven months from May 2018 to June 2019. A total 65 Multiple Myeloma (MM) patients(with age range of 39- 81years) were involved in the study who were subjected to physical examination and diagnosed by hematologists with Multiplemyeloma from both genders (based on the Diagnostic criteria of the International Myeloma Working Group - IMWG). They were distributed to different Departments of hematology from Al-Imamain Al-Kadhimain Medical City, Al-Yarmuk Hospital, Baghdad Medical City teaching laboratories, Mirjan teaching Hospital in Hilla, and center of hematology and oncology in Basra.

A group (12) of newly diagnosed pattients emerged. The 65 patients were grouped into 3 stages according to the international staging system (ISS):Group **A – Stage I** (21 patients, age mean 57.14±12.25 years), Group **B – Stage II** (22 patients, age mean of 56.45±11.33 years), and Group **C-Stage III**(22 patients, age mean 60.59±11.55 years).

Full data were obtained from each patient using a preformed questionnaire. Initial laboratory results were recorded from tests performed for the patients. Serum urea, creatinine, and calcium were determined by spectrophotometric method. Moreover, a complete blood count and ESR, serum Immuno- fixation Electrophoresis, Imaging bone surveys, bone marrow aspirate, and bone marrow biopsy results were registered for each patient. Patients excluded from the study were those who had Liver disease, active infections (human immune-deficiency virus, HIV, Hepatitis B, or C), and pregnant or breast-feeding women. For each patient the following laboratory tests were done: Serum albumin, and protein electrophoresis, Free light chains test Kappa (FLC-k) & Lambda (FLC-l), β2microglobulin (β2-MG), Osteocalcin (OC), C-terminal telopeptide (CTX), Beta C-terminal telopeptide (βCTX), Parathyroid hormone (PTH) and Syndecan-1(CD138). All tests were done by ELISA technique.

Results

None of the included demographic characteristics like age, gender, BMI, as well as residency showed any significant association with any of the three stages of the disease, (as shown in table 1).

Table (1): Association of Demographic Characteristics of The Patients and duration with Disease Staging

Variables	Stage I (n=21)	Stage II (n=22)	Stage III (n=22)	P-value
Age (Years) Mean±SD	57.14±12.25	56.45±11.33	60.59±11.55	0.461
Gender				
Male	14(66.67%)	12(54.55%)	15(68.18%)	0.593
Female	7(33.33%)	10(45.45%)	7(31.82%)	
BMI (kg/m^2)	22.83±3.88	21.36±3.29	22.73±4.05	0.359

Variables	Stage I (n=21)	Stage II (n=22)	Stage III (n=22)	P-value
Residence				
Urban	9(42.86%)	8(36.36%)	14(63.64%)	0.168
Rural	12(57.14%)	14(63.64%)	8(36.36%)	
Weight				
Underweight	4(19.05%)	4(18.18%)	5(22.73%)	
Normal weight	12(57.14%)	15(68.18%)	8(36.36%)	0.589
Overweight	4(19.05%)	2(9.09%)	8(36.36%)	
Obese	1(4.76%)	1(4.55%)	1(4.55%)	
Duration (Months)				
Mean±SD	6.19±2.96[a]	15.73±10.45[b]	35.04±31.78[c]	0.00

[a, b and c]different small letters indicate significant differences.

For the bone markers the Univariate Cox progression analysis showed that only CTX and βCTX had a significant association with disease progression with P-values of 0.023 & 0.044 respectively (table 2).

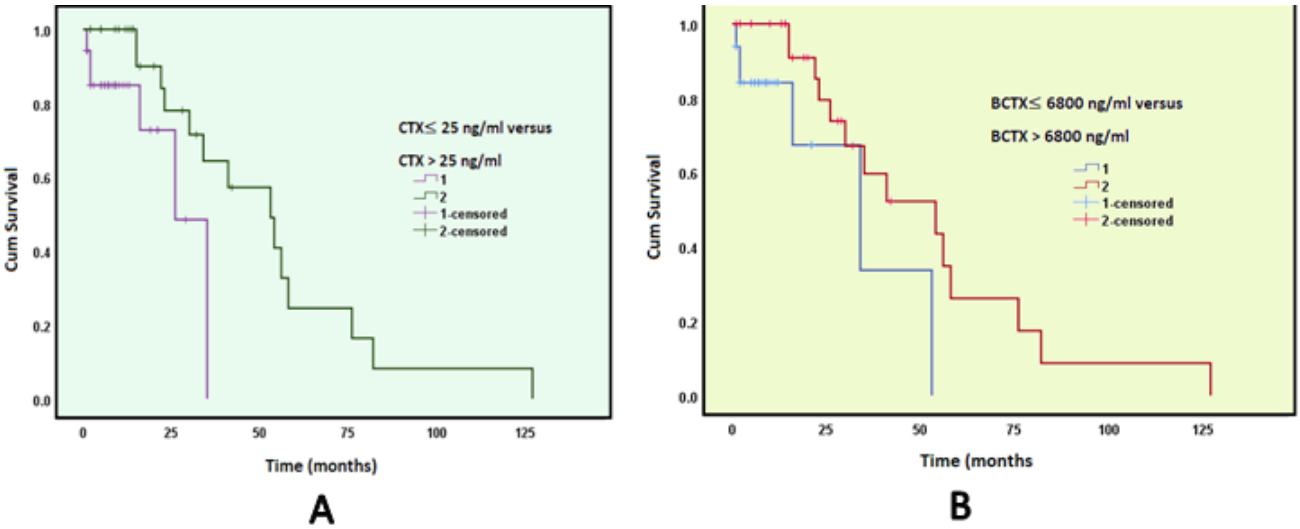

Figure 1: (A) : Kaplan-Meier curve. Mean time in advanced stage for β CTX <6800 & > 6800 ng/mL; (B): Receiver Operating Curve for Some Selected Markers in The Context of Discrimination between Newly Diagnosed and Longstanding MM patients

Kaplan-Meier survival curve was constructed to find out the prognostic value of CTX and βCTX in free-progression survival (FPS). Mean FPS for patients with CTX ≤ 25 ng/ml was 52.86 months (95%CI= 36.93-68.78), while that for CTX > 25 ng/ml it was 25.46 months (95%CI= 19.0-31.91), p-value (Log-Rank) = 0.015 (Figure 1-A).

Likewise, mean FPS for patients with βCTX ≤ 6800 ng/ml was 52.51 months (95%CI= 35.97-69.06), while that for βCTX >6800 ng/ml= 32.26 months (95%CI= 18.48-46.03) p-value (Log-Rank) = 0.014 (Figure 1-B).

Table 2: Univariate Cox Regression Analysis of bone turnover markers as Risk for MM progression

Variable	p-value	HR	95%CI
FLCλ(ng/ml) ≤30, >30	0.267	0.43	0.1-1.91
FLCκ (ng/ml) ≤30, >30	0.816	1.14	0.37-3.5
Total FLC (ng/ml) ≤60, >60	0.154	1.60	0.37-6.82
κ/λ ratio ≤2.5, >2.5	0.154	2.62	6.7-9.86
PTH (pg/ml) ≤150, >150	0.851	1.1	0.37-3.25
Osteocalcin (mg/dl) ≤10, >10	0.338	0.36	0.04-2.9
CTX (ng/ml) ≤25, >25	0.023	4.65	1.23-17.62
βCTX (ng/ml) ≤6800, >6800	0.044	3.61	1.03-12.57
CD138 (ng/ml) ≤400, >400	0.179	2.53	0.65-9.81

The patients of the study were divided into two groups regardless of staging: newly diagnosed (12 cases) and longstanding (43 cases). The bone turnover markers which show significant differences between newly diagnosed and longstanding patients are (shown in table -3).

Table 3:Bone markers in Newly Diagnosed & Longstanding MM Patients

Variables	Newly diagnosed (n=12)	Longstanding (n=53)	P-value
FLCκ (ng/ml)	8.81±7.91	32.65±25.76	0.002
FLCλ (ng/ml)	9.88±6.57	35.03±32.74	0.011
PTH (pg/ml)	174.5±15.0	150.36±29.94	0.009
κ/λ ratio	3.98±9.53	2.11±1.7	0.175
Total FLC (ng/ml)	18.69±5.35	67.68±26.46	<0.001
Osteocalcin (ng/ml)	10.39±9.2	9.56±5.13	0.668
CTX (ng/ml)	22.6±4.63	24.42±8.04	0.454
βCTX (ng/ml)	6380±1388	6926.2±2413	0.454
CD138 (ng/ml)	262.58±90.76	428.17±190.85	0.005

The Receiver operating characteristic (ROC) curve was used to evaluate the diagnostic value for the detection of new MM cases. Figure s 3 & 4 show the results of ROC curve in the evaluation of FLCκ, FLCλ, total FLC and CD 138.

The CD138 showed significant increase in the longstanding patients compared with the newly diagnosed patients, The AUC was 0.742, 95%CI= 0.49-0.951, p=<0.001. The sensitivity and specificity of the test at CD38 cut off= 345.35 ng/ml were 0.922 and 0.73 respectively.

Discussion

About 80% of newly diagnosed MM patients were reported to have bone disease (osteoporosis osteolysis or compression fractures) with spine being the more frequent site affected[21]. The present results show the significant association of CTX and βCTX with disease progression. Recent study has attributed osteoporosis of MM to imbalance of osteoclast and osteoblasts which results in increased production of βCTX and show very high concentration in the third stage of MM[22] .

They were claimed to be useful in assisting clinicians to evaluate a patient's risk of developing complications during healing following surgical intervention[23], moreover it was reported to show significant change in MM before progressive disease were recognized [24]. Another report on the clinical importance of urine N- terminal telopeptide (NTx) and serum C- terminal telopeptide (CTX) showed that these markers, with osteocalcin and bone alkaline phosphatase, were very important in the prognosis of MM[25].

The present finding of Kaplan-Meier curve on carboxy telopeptide being a predictor of overall survival in the myeloma patients coincides with previous reports[26]. Thomas Lund et al, 2010, went further to consider these markers important tools for patient therapy and management and others claimed that high CTX would predict for poor overall survival in MM patients on some type of therapy[27].

In the comparison between the newly diagnosed and longstanding patients, and the measurement of sensitivity and specificity of the bone markers which showed significant differences, the clinical importance of total free light chain and their two types (FLCκ, & FLCλ,) is clearly evident (fig. 1).

In addition of being a marker for clonal evolution of the neoplastic cells it also indicates a loss of control on heavy and light chains synthesis[28]. However, recent report recommended the use of serum FLC ratio with caution and abnormal serum FLC ratio should be limited to those who have high Light chain only[29].

Syndecan (CD138) is among the markers which showed a significant difference between the newly diagnosed and long-standing MM patients with acceptable sensitivity and specificity (fig 1).

Syndecanis a member of a family of integral membrane heparin sulfate proteoglycans. It is detected solely on cells of the B lymphocyte lineage[30].

The results of a recent study show that squamous cell (and urothelial) carcinomas are prone to express Syndecan-1, often at high levels. The CD138 expression analysis is currently used in routine diagnostic pathology to distinguish and quantitate plasma cells, for example, in the bone marrow and in endometrial biopsies where the presence of plasma cells indicates chronic endometritis[29]. The surface expression of CD138 was reported to dynamically regulates a switch between growth and dissemination for myeloma, in response to nutrient conditions[30] .

Conclusions

All the studied markers could be used collectively to give better detection, prognosis and discrimination between newly diagnosed and long-standing patients, but, however the total FLC remains the best.

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References

1. Firth J . Multiple myeloma: Haematology, Clinical Medicine CME medical masterclass, 2019;19(1): 19.
2. Heider U, Fleissner C, Ivana Zavrski I, Kaiser M, Hecht M, Jakob C, Sezer O .Bone markers in multiple myeloma. Eur J Cancer . 2006;42(11):1544-53.
3. Moreau P, Miguel JS, Sonneveld P, Mateos MV, Zamagni, and Avet-Loiseau H. Multiple Myeloma: ESMO Clinical Practice Guidelines. Ann Oncol . 2017; 28 (suppl 4): iv52–iv61.
4. Palmer SR, Erickson LA, Ichetovkin I, Knauer DJ, Markovic SN. Circulating serologic and molecular biomarkers in malignant melanoma. Mayo Clin Proc. 2011;86(10):981–90.
5. Nandakumar B, Binder M, and Dispenzieri A. Continued improvement in survival in multiple myeloma (MM) including high-risk patients. Presented at: American Society of Clinical Oncology Annual Meeting; May 31-June 4, 2019; Chicago, Illinois. Suppl Abstract 8039.
6. Chia-Siu W. CRP and malignancy Clinico-pathological association and therapeutic implication. Chang Gung Med J 2009; 32:471-82.
7. Eleftherakis-Papapiakovou E, Kastritis E, and Roussou M, Renal impairment is not an independent adverse prognostic factor in patients with multiple myeloma treated upfront with novel agent-based regimens. Leukemia & lymphoma. 2011;52(12):2299–2303.
8. Derman BA, Jasielec J, Langerman SS, Zhang W, Jakubowiak AZ & . ChiuBC,Racial differences in treatment and outcomes in multiple myeloma: a multiple myeloma research foundation analysis Blood Cancer Journal 2020; 10 : 80,.
9. Kim SM, Kim MJ, Jung HA, Kim K, Kim SJ, Jang JH, Won Seog Kim WS, and Jung CW . Comparison of the Freiburg and Charlson Comorbidity Indices in Predicting Overall Survival in Elderly Patients with Newly Diagnosed Multiple Myeloma,Biomed research international. 2014, ID 437852.
10. Saburi M, Ogata M, Soga Y, Kondo Y, Kurimoto R andItani K.Poor response to daratumumab and carfilzomib in newly diagnosed anaplastic multiple myeloma,J Clin Exp Hematop. 2020;60(1):17-20.
11. Gupta N, Sharma A, Sharma A . Emerging biomarkers in Multiple Myeloma: A review; Clinica Chimica Acta 2020, 503 : 45-53 .
12. Filho AGO, Carneiro BC, Pastore D, Silva IP, Yamashita SR. and Consolo FD, Whole-Body Imaging of Multiple Myeloma: Diagnostic Criteria, Radio Graphics, 2019,Vol. 39, No. 4.
13. Rajkumar SV. Multiple myeloma: 2014 Update on diagnosis, risk-stratification, and management; American J. hematology 2014 (89): 998-1009.
14. Hutchison CA, Batuman V, Behrens J, Bridoux F, Sirac C, The pathogenesis and diagnosis of acute kidney injury in multiple myeloma, Nat Rev Nephrol. 2011; 8(1):43-51.
15. Russell SJ, Rajkumar SV. Multiple myeloma and the road to personalised medicine. Lancet Oncol 2011; 12: 617– 619.
16. Kyle RA, RemsteinED,Therneau TM, Dispenzieri A, Kurtin PJ, and Hodnefield JM. Clinical Course and Prognosis of Smoldering (Asymptomatic), Multiple Myeloma. N. Engl J Med 2007; 356:2582-2590.
17. Lin Q, Zhao J, Song Y & Liu D. Recent updates on CAR T clinical trials for multiple myeloma,

Molecular Cancer 2019, 18 (1): 154.

18. Auzina D, Erts R., Lejniece S. Prognostic value of the bone turnover markers in multiple myeloma, Experimental oncology. 2017; 39 .
19. Marx, RE, et al. Oral Bisphosphonate-Induced Osteonecrosis: Risk Factors, Prediction of Risk Using Serum CTX Testing, Prevention, and Treatment, J OralMaxillofac Surg. 2007;65:2397-2410.
20. Lund T, Abildgaard N, Thomas L, Andersen TL, Delaisse JM, and Plesner T, Multiple myeloma: changes in serum C-terminal telopeptide of collagen type I and bone-specific alkaline phosphatase can be used in daily practice to detect imminent osteolysis, Eur J Haematol. 2010; 84(5): 412–420.
21. Terpos E, Christoulas D, Kastritis E, Papatheodorou A, and Kanellias N.. High C-Terminal Cross-Linking Telopeptide of Collagen Type-I (CTX) Predicts for Poor Overall Survival in Patients with Multiple Myeloma Who Receive Frontline Therapy with Immunomodulatory Drugs (IMiDs) but Not with Bortezomib-Based Regimens, Blood. 2012; 120(21): 935.
22. Faraz S, Pearse RN, Yadlapati S, Jayabalan D, Rossi AC, and Mark TM, The clinical Utility of Bone Resorption and Bone Formation Markers in Multiple Myeloma; Blood. 2015; 126 (23): 5373.
23. Schiano C, Soricelli A, De Nigris F. and Napoli C. New challenges in integrated diagnosis by imaging and osteo-immunology in bone lesions. Expert review of clinical immunology. 2019;15(3):289-301.
24. Wang X. The mechanism and traditional Chinese medicine research of bone destruction and hypercalcemia in multiple myeloma. TMR Theory and Hypothesis. 2019; 2(3):225-8.
25. Jakob C, Liebisch P, Heider U, Kaiser M, and Sterz J, Incorporation of the Bone Marker Carboxy-Terminal Telopeptide of Type-1 Collagen (ICTP) into a Combined ISS-ICTP Score Improves the Prognostic Significance of the ISS in Newly Diagnosed Symptomatic Multiple Myeloma and Identifies a Very Low Risk Group Which Has No Benefit from High-Dose Therapy, Blood. 2008; 112 (11): 2721
26. Kumar S, Larson DR, Dispenzieri A, Therneau TM, Murray DL, Bergsagel PL, Kyle RA, Rajkumar SV. Polyclonal serum free light chain elevation is associated with increased risk of monoclonal gammopathies. Blood cancer journal. 2019;9(6):1-6.
27. Abdallah N, Kapoor P, Murray DL, Buadi FK, Dingli D, Dispenzieri A, et al 'Utility of serum free light chain ratio in response definition in patients with multiplemyeloma, Blood Adv. 2020; 4 (2): 322–326.
28. Seidel C, Sundan A, Hjorth Mand Turesson ISerum syndecan-1: A new independent prognostic marker in multiple myeloma Blood 2000, 95(2):388-92,
29. Kind S, Merenkow C, Büscheck F, Möller K, Dum D. abd Viktoria ChiricoV. Prevalence of Syndecan-1 (CD138) Expression in Different Kinds of Human Tumors Normal Tissues, Research article. 2019; ID 4928315.
30. Akhmetzyanova I, McCarron MJ, Parekh S, Chesi M, Bergsagel PL. and Fooksman DR. Multiple myeloma gammopathies Dynamic CD138 surface expression regulates switch between myeloma growth and dissemination .Leukemia. 2020;34:245-356.