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Table of Contents

Original Articles

Review Article

Conference Highlights/Scientific Contributions

Original Study

Exploring the Clinicopathological Parameters Affecting the Outcome in Egyptian Patients with Multiple Myeloma

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Abstract

Background

Multiple myeloma (MM) is a plasma–cell neoplasm in which the interplay of several clinical, pathological and genetic parameters affects the patient's prognosis and response to treatment and survival.

Aim

The aim of this study was to evaluate the different clinicopathological parameters of MM patients in correlation with response to therapy, progression–free survival (PFS) and overall survival (OS).

Methods

This retrospective study was performed on 60 MM patients diagnosed at NCI, Cairo University from January 2005 to December 2008. The patients were evaluated for different clinicopathological parameters which were correlated to their response to treatment, OS and PFS.

Results

Sixty patients were followed up for a median period of 21 months wherein about 90% received 1st line treatment: 34 VAD, 17 MP and 3 dexamethasone. Six patients (10%) were referred for BSC. CR was achieved by 15%, 11.7% achieved good PR, 6.7% achieved PR, 22.1% have stable disease, 35% experienced disease progression.

ECOG PS–I patients have 39 months median survival compared to 12 months for patients with PS ECOG–II (P 0.005). Patients with multiple skeletal lesions (≥3) have median OS of 19 months (P 0.03). Patients who presented with plasmacytoma have better OS than those without (38 months versus 14 months) (P< 0.05).

Patients <60 years old have a better median OS compared to patients >60 years (37 months versus 12 months) (P 0.001). OS was 39 months in female patients versus 14 months in male patients (P0.025).

Median OS was 9 months for patients with co–morbidities versus 27 months for those without (P 0.01), 39 months for patients with non–detected paraproteinuria versus 18 months for those with paraproteinuria (P 0.045), 18 months for stage II disease versus 12 months for stage III disease (P 0.001), 12 months for patients with elevated serum LDH versus 39 months for those with normal levels (P 0.001), 27 months for patients with normal serum creatinine level versus 13 months for those with elevated levels (> 1.4 mg/dl) (P 0.005), 27 months for patients with normal serum calcium levels versus 10 months for those with hypercalcemia (P 0.03).

Conclusion

Besides FISH–guided molecular cytogenetic classification of myeloma abnormality, a specific risk–stratification model based upon the patient's age, sex, performance status, lytic bone lesions, plasma cells labeling index, serum creatinine, calcium, LDH, B2M and paraproteins in serum and urine, can depict the response to treatment, OS and PFS of patients with MM.

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استكشاف المتثابتات الباثولوجية الإكلينكية المؤثرة على محصلة الإصابة بالورم النقوي المتعدد في المرضى المصريين

الخلفية

الورم النقوي المتعدد (MM) **هو تنشؤ خلايا البلازما ، تتداخل فيه متثابتات إكلينيكية وباثولوجية ووراثية عددية وتؤثر على مآل المرضى والاستجابة للعلاج وكذلك للبقيا .**

الهدف : الهدف من هذه الدراسة هو تقييم المتثابتات الباثولوجية الإكلينيكية المختلفة لمرضى الورم النقوي المتعدد لدينا، وربطها بالاستجابة للعلاج، البقيا الخالية من تقدم المرض (PFS) **والبقيا العامة .**

الطرق

تم إجراء هذه الدراسة الاستعادية على 60 مريض مصاب بالورم النقوي المتعدد وقد شُخصت هذه الإصابة بمعهد الأورام – جامعة القاهرة من يناير 2005 إلى ديسمبر 2008 . تم تقييم المرضى بالنسبة لمتثابتات باثولوجية إكلينيكية مختلفة تتعلق بالاستجابة للمعالجة والبقيا العامة والبقيا الخالية من تقدم المرض .

النتائج

تم متابعة 60 مريض خلال فترة ناصفة تقدر بـ 21 شهراً ، 90 % منهم تلقى المعالجة بالخط الأول وهي كالتالي

(3) ، (MP 17) ، (VAC 34) ديكساميثازون) . تم إحالة ستة من المرضى إلى (اسم لمستشفى آخر) BSC ، حقق 15 % منهم هدأة كاملة ، بينما 11.7 % لديهم هدأة جزئية جيدة ، 6.7% هدأة جزئية ، 22.1 % لديهم مرضى مستقر ، 35 % عانوا من تطور المرض لديهم .

ECOGPS-I وحسب تصنيف الجمعية الشرقية لعلم الأورام (المرحلة I): كانت البقيا الناصفة لدى المرضى = 39 شهرا بالمقارنة بالمرضى ذو ECOG-II كانت 12شهرا (P = 0.005) (الاحتمالية = 0.005) ، المرضى ذوو الآفات الهيكلية المتعددة (>3) كانت لديهم البقيا العامة الناصفة = 19 شهراً (P 0.03). بينما المرضى الذين تجلوا بورم البلازماويات كانت البقيا العامة لديهم أفضل من غيرهم (38 شهرا مقابل 14 شهرا) (P >0.05) .

المرضى أقل من 60 عاما كان لديهم البقيا العامة الناصفة أفضل مقارنة بالمرضى أكبر من 60 عاما (37 شهرا مقابل 12 شهراً) (P= 0.001) ، بينما كانت البقيا العامة لدة المرضى الإناث = 39شهرا مقابل 14 شهرا لدى لمرضى الذكور (P= 0.025)

كانت البقيا العامة الناصفة لدى المرضى بوجود إمراضيات مشاركة 9 شهور مقابل 27 شهرا لأولئك المرضى بدون إمراضيات ، كذلك كانت 39 شهرا للمرضى غير محدد وجود البارابروتين في البول لديهم مقابل 18 شهرا لأولئك المرضى مع وجود البارابورتين في البول (P 0.045) ، و 18 شهرا للمرضى من المرحلة الثانية II مقابل 12 شهرا للمرحلة III في المرضى (P 0.001) ، و 12 شهرا للمرضى مع وجود نزعة الهيدروجين اللاكتاتية المصلية المرتفعة مقابل 39 شهرا للمرضى مع وجود مستوى طبيعي منها (P 0.001) ، و 27شهرا للمرضى مع مستوى الكرياتينين المصلي طبيعي مقابل 13 شهرا للمرضى مع مستوى مرتفع منه (< 1.4 ملجرام / ديسي لتر) 27 ، (P0.005) شهرا للمرضى مع وجود مستوى الكالسيوم في المصل طبيعي مقابل 10 شهور للمرضى مع فرط كلس الدم (P 0.03) .

الخلاصة

بالإضافة إلى التصنيف الخلوي الجزئيي المّوجه بالتهجين في الموضع التألقي (FISH) **لشذوذات الورم النقوي ، فإن هناك نموذج تدّرج الاختطار والمرتكز على عمر المريض وجنسه وحالة الأداء والآفات الحالة للعظام ، ومنسب التوسيم للخلايا البلازماوية ، وكرياتينين المصل والكالسيوم و نازعة الهيدروجين اللاكتاتية ، الجلوبولين المكروي B2 و البارابورتين في المصل والبول ، كل هذه المتثابتات تصنع لنا تصورا للمعالجة والبقيا العامة والبقيا الخالية من تقدم المرض للمرضى المصابين بالورم النقوي المتعدد .**

FISH = Fluorescence In Situ Hybridization.

Introduction

Multiple myeloma (MM) accounts for 10% of all hematologic cancers.[9, 10] The age–adjusted annual incidence of MM is 4.3 cases per 100,000 white men, 3 cases per 100,000 white women and 9.6 cases per 100,000 black men. The disease is characterized by neoplastic proliferation of plasma cells involving >10% of the bone marrow (BM). Increasing evidence suggests that BM microenvironment of tumor cells plays a pivotal role in the pathogenesis of MM.[4] This information has resulted in the expansion of treatment options.

Plasma cells are characterized by overproduction of monoclonal immunoglobulin G (IgG), immunoglobulin A (IgA) and/or light chains which may be identified by serum protein electrophoresis (SPEP) or urine protein electrophoresis (UPEP). BM infiltration by plasma cells results in neutropenia, anemia and thrombocytopenia. In terms of bleeding, M components may interact specifically with clotting factors leading to defective aggregation. Plasma cell proliferation causes extensive skeletal destruction with osteolytic lesions, anemia and hypercalcemia. Isolated plasmacytomas (which affect 2–10% of patients) lead to hypercalcemia through production of the osteoclast–activating factor. Destruction of bone and its replacement by tumor may lead to pain, spinal cord compression and pathologic fracture with bony involvement typically lytic in nature. The most common mechanisms of renal injury in MM are direct tubular injury, amyloidosis or involvement by plasmacytoma. [5, 6] Renal conditions that may be observed include hypercalcemic nephropathy, hyperuricemia due to renal infiltration of plasma cells resulting in myeloma, light–chain nephropathy, amyloidosis, and glomerulosclerosis.

The disease is heterogeneous with rapid progression in some patients despite treatment, while others do not require therapy for a number of years. The prognosis of patients with myeloma is dependent on four key factors: tumor burden (staging), patient factors, disease biology, and aggressiveness and response to therapy [1]. Tumor burden and proliferation rate are the 2 key indicators for prognosis. Many schemas have been published to aid in determining the prognosis. One schema uses C–reactive protein (CRP) and beta–2 microglobulin (B2M) to predict survival [12].

Poor prognostic factors include tumor mass, hypercalcemia, Bence Jones proteinemia, and renal impairment. In fact, it seems that new agents such as bortezomib can overcome the negative impact of poor cytogenetics [35–37]. With the use of conventional chemotherapy, the median survival of patients with MM has been 3 years [1–3] and the proportion of long–term survivors is disappointingly small [4, 5]. However, there is wide variability in survival, which is due to differences related to both the host and the tumor.

Two main staging systems exist: the International staging system (ISS) and the Durie–Salmon staging system. These staging systems are predominantly used to stratify patients enrolled in clinical trials and allow clinicians to better interpret and compare such trials. Other prognostic studies, such as BM cytogenetics and studies of chromosomal translocations, are more frequently used to determine the preferred treatment approach. With conventional therapy, the OS is approximately 3 years, and event–free survival (EFS) is < 2 years. With high–dose chemotherapy and stem–cell transplantation, the OS rate is > 50% at 5 years. Bacterial infection is the leading cause of death in patients with MM.[1, 26]

Before the introduction of novel agents, a limited number of patients treated with conventional chemotherapy achieved a complete response (CR) and the correlation between the degree of response and survival was questioned in several studies[38–41] In fact, in many studies, the stabilization of the disease was a more powerful prognostic indicator than the degree of the tumor decrease.[38, 40, 41] Contrasting with the low CR rate achieved with conventional chemotherapy, about one–third of patients achieve an immunofixation–negative CR after high–dose therapy/stem cell transplantation (HDT/SCT).[41]

Interestingly, a correlation between the depth of response and survival has been shown after HDT/SCT.[43–46] In this regard, patients entering CR following HDT/SCT have a significantly higher EFS and OS than those who only enter partial response (PR) or do not respond.[44, 45] While this would suggest that there is a difference in the quality of response to conventional chemotherapy and after high–dose therapy, the EFS and OS of patients achieving CR were similar in the MD Anderson experience, irrespective of whether CR was achieved with conventional therapy or with HDT/SCT.[40, 41] This has raised a still

unsolved question: Do patients already in CR with conventional chemotherapy benefit from high–dose therapy intensification? With the incorporation of novel agents, particularly thalidomide, bortezomib and lenalidomide in the upfront setting, a significant number of patients achieve CR with primary therapy[35] A longer follow–up is needed to establish the impact of these CRs on EFS and OS in non–transplant patients. Additionally, the incorporation of new drugs in the induction pre–transplant regimens results in a higher tumor reduction and this will hopefully result in a higher post–transplant CR rate. However, the impact of new drugs on the post–transplant outcome remains to be determined.

The aim of this study is to evaluate the different prognostic factors of our MM patients and to correlate them with their response to therapy, PFS and OS.

Patients and Methods

This study was performed retrospectively on 60 MM patients diagnosed at the Medical Oncology Department of the National Cancer Institute, Cairo University for a period of 4 years, from January 2005 to December 2008. All the patients were evaluated for different prognostic factors as follows: (1) Age: below or above 60 years, (2) Gender, (3) ECOG Performance status, (4) Paraprotein level, (5) Hemoglobin level, (6) Serum calcium level, (7) Number of lytic bony lesions, (8) Serum albumin level, (9) B2–microglobulin level, (10) Serum LDH, (11) Percentage of plasma cells in BM, and (12) Serum creatinine level. Revision of chemotherapy and radiotherapy given to these patients and response to treatment were evaluated. PFS and OS were calculated and correlated with different prognostic factors.

The diagnosis of MM required a minimum of 1 major and 1 minor criterion, although (1) + (a) is not sufficient, or 3 minor criteria that must include (a) and (b).

Major criteria:

1. Plasmacytomas on tissue biopsy
2. Bone marrow plasmacytosis (>30% plasma cells)
3. Monoclonal immunoglobulin spike on serum or urine electrophoresis: IgG>3.5 g/dL or IgA >2.0 g/dL; light chain urinary excretion >1.0 g/day.

Minor criteria:

1. Bone marrow plasmacytosis (10% to 30%)
2. Monoclonal immunoglobulin spike present but at a lower magnitude than above
3. Lytic bone lesions
4. IgM>500 mg/L, IgA >1000 mg/L (>1 g/L), or IgG>6 g/L.

Patients with the above criteria associated with one of those below are categorized as having indolent myeloma and do not require immediate therapy:

- Absent or limited bone lesions (3 or fewer lytic lesions), no compression fractures
- Stable paraprotein levels IgG<70 g/L, IgA <50000 mg/L (<50 g/L)
- No symptoms or associated disease features including Karnofsky's performance status >70%, hemoglobin>10 g/L, normal serum calcium, serum creatinine<2 mg/dL and no infections
- Plasma cell labeling index less than or equal to 0.5%.

Statistical analysis

Data was analyzed using SPSS Windows statistical package version 17 (SPSS Inc., Chicago, IL). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Chi–square test (Fisher's exact test) was used to examine the relation between qualitative variables. Survival analysis was done using Kaplan–Meier method and comparison between two survival curves was done using log–rank test. A p–value < 0.05 was considered significant.

Results

Clinicopathological characters of the patients:

The clinicopathological characters of MM patients are shown Table 1. Most of the patients (48/60, 80%) were under 60 years. Male to female ratio is 3 to 2 and most of them had PS–1 (56.7%). A significant portion had co–morbidities (19/60, 31.7%) and 2/60 (3.3%) presented with renal failure. In addition, 46/60 (76.7%) have more than 3 skeletal lesions.

Median age of patients was 55 years (42–70), median hemoglobin 10 (4.7–15), median serum

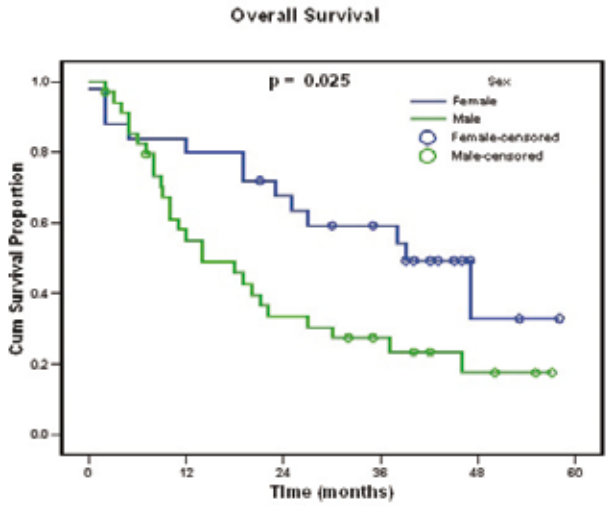

Figure 1. OS of MM patients according to gender

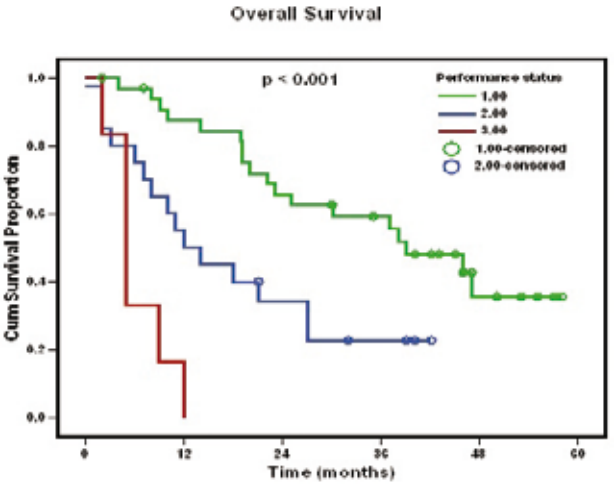

Figure 2. OS with regards to PS

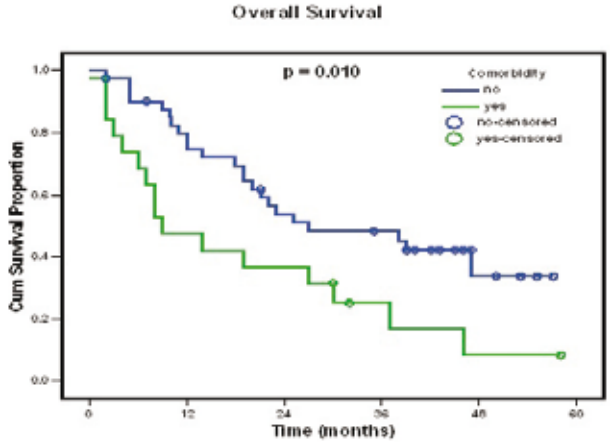

Figure 3. OS of MM patients according to comorbidity: Hypertension, IHD, DM, COPD, CVS, renal failure as well as chronic liver disease.

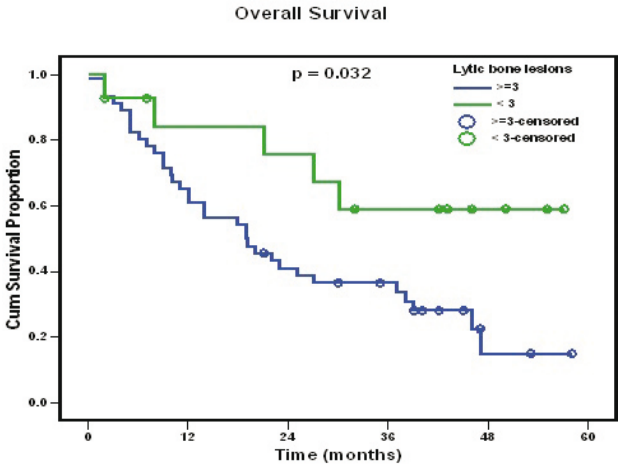

Figure 4. OS of MM patients according to bony lesions

albumin was 3.2 (1.–4.1), median B2M was 4.6 (1.3–13), median LDH was 466 (245–3726), calcium 9.9 (8–16), creatinine 1 (0.6–13). Median plasma cells % in the BM was 20% (1–78). Median Follow–up time was 21 months (0–58).

Details of Treatment and response:

1st line: 54/60 (90%) patients received 1st line treatment of which 34 (56.7%) received VAD, 17 (28.3%) received MP and 3 (5%) dexamethasone. Radiotherapy was given in 56.7% of 1st line cases, Bisphosphonates were given to 43.3% of cases, 10% were referred to the pain clinic and received best supportive treatment, 8.5% developed complications from the 1st line treatment, 15.3% achieved CR, while good PR was achieved in 11.9% of cases, 6.8% achieved PR, progression occurred in 35.5% while 22% had a stable disease.

2nd line: 42/60 (70%) of the cases received 2nd line treatment of which 1 patient (2.4%) received CVP, another patient (2.4%) received Thalidomide–Dexamethasone, 8 patients (14.3%) received VAD, 15 patients (26.2%) received DCEP, 30 patients (50%) received MP, 8 patients (14.3%) received Radiotherapy, 30 patients (50%) received Bisphosphonates, and 1 patient (2.4%) received Dexamethasone as a single agent.

3rd line: Third line treatment was given to 27 patients (45%) of which 25.9% received MP, 22.2% received Dexamethasone single agent, 29.6% received Thalidomide–Dexamethasone, 14.8%

Factor	Category	No	%
Age	>60	48	80
	<60	12	20
Sex	Male	35	58.3
	female	25	41.7
ECOG PS	I		56.7
	II		33.3
	III		10
Co–morbidity	Co–morbidity	19	31.7
DM, HTN, COPD, CLD	No co–morbidity	41	68.3
Skeletal lesions	Skeletal lesions ≥ 3	46	76.7
	Skeletal lesions < 3	14	23.3
Paraplegia	Yes	1	1.7
	No	59	98.3
Renal failure	Yes	2	3.3
	no	58	96.7
Plasmacytoma	Present	28	46.7
	Absent	32	53
S. Creatinine level	> 1.4 mg/dl	11	18.3
	<1.4 mg/dl	49	81.7
Paraproteins in urine	Detected		85
	Not detected		15
Anemia	Hb< 12.5 gm%	53	88.3
	Hb> 12.5 gm%	7	11.7
Plasma cells in BM	Elevated		43.3
	Not elevated		56.7
B2M	>2	52	86.7
	Up to 2	8	13.3
Serum Albumin	< 3.5gm%	45	75
	> 3.5gm%	15	25
LDH	>480	26	43.3
	Up to 480	34	58.7
serum Calcium	> 11.5 mg/dl	11	18.3
	< 11.5 mg/dl	49	81.7

Table 1. Clinicopathological characters of the multiple myeloma patients included in this study.

	VAD	MP	Thal–Dex.	CVP	DCEP	Dex	Bis.	RTH
1st line treatment	33 (56.7%)	17 (28.3%)				3 (5%)	26 (43.3%)	34 (56.7%)
2nd line treatment	9 (14.3%)	30 (50%)	1 2.4%	1 2.4%	16 26.2%	1 2.4%	30 50%	9 14.3%
3rd line treatment		15 25.9%	18 29.6%		9 14.8%	13 22.2%	38 63%	9 14.8%

Table 2. Treatment regimens given to MM patients.

10% of the cases were referred to the pain clinic seeking further management regarding their pain.
8.5% of the cases who received 1st line ttt developed complications and ttt was omitted.

received DCEP, 63% received Bisphosphonates, and 14.8% received radiotherapy.

Overall survival:

Patients <60 years have a better OS than patients >60 years (median 37 months versus 12 months) (P 0.001). Median OS was 39 months in female patients versus 14 months in male patients (P0.025) (Figure 1). Patients with PS ECOG–I had a median survival of 39 months compared to 12 months for patients with PS ECOG–II (P 0.005) (Figure 2). Median OS was 9 months for patients with co–morbid disease while 27 months for patients with no co–morbidity (P 0.01) (Figure 3). Patients with multiple skeletal lesions (≥3) have a median OS of 19 months (P 0.03) (Figure 4). Patients presented with pathological fracture have OS less than those patients who did not experience pathological fractures (median 19 months versus 27 months) (P 0.11). Patients who presented with plasmacytoma have better median OS than those presented without (38 months versus 14 months) (P 0.05).

Median OS for patients with elevated serum paraprotein level was 22 months (P–value 0.27). Median OS was 39 months for those with non–detected paraprotein in urine versus 18 months for those patients who experienced para proteinuria (P 0.045). OS for patients who presented with hemoglobin level <12.5 gm/dl was 22 months. Median OS for patients with hypoalbuminemia (<3.5 gm/dl) was 19 months and not reached for those with albumin ≥3.5 gm/dl (P 0.006). Median OS for patients with elevated B2M was 19 months and not reached in those patients with B2M >2 (P–value 0.02). For stage II disease median OS was 18 months versus 12 months for stage III disease (P 0.001). Median OS for patients with elevated serum LDH was 12 months versus 39 months for those who experienced normal levels of serum LDH (P 0.001). Median OS for patients with plasma cell percentage <5% was 46 months versus 20 months for those patients who have plasma cell % in BM >5% (P 0.14). Median OS was better in patients who presented with normal serum calcium levels than those presented with hypercalcemia (27 months vs. 10 months) (P 0.03). Median OS for patients with normal serum creatinine level was 27 months versus 13 months for patients presented with elevated serum creatinine level (>1.4 mg/dl) (P 0.005).

PFS:

Median PFS was nearly equal in both age groups (6 months) (P 0.14). For female patients, it was 7 months vs. 6 months for male patients (P 0.88). Median PFS was better in patients with less than 3 lytic bony lesions (8 months versus 6 months) than those patients who presented with ≥3 bony lesions (P 0.08) and was better in patients with non–detected paraprotein level (5 months vs. 7 months) than those with detected paraprotein level. Median PFS was 25 months for patients with hemoglobin level ≥ 12.5 gm/dl while it was only 6 months for those with hemoglobin level < 12.5 gm/dl. (P 0.09), and it was 7 months for those patients with normal albumin level versus 5 months for patients with low albumin

Ttt line	Percent of cases received ttt	CR	GPR	PR	SD	PD	complications
1st line	90%	15.3%	11,9%	6.8%	22%	35.5%	8.5%
2nd line	66.7%	2.5%	20%	–	30%	47.5%	–
3rd line	43.3%	–	–	19.2%	42.3%	38.5%	–

Table 3. Response to treatments given for MM patients.

CR: complete response, GPR: good partial response, PR: partial response, SD: stable disease RR: response rate, PD: progressive disease. ttt: treatment.

level (P– 0.29). It was 6 months for patients with elevated serum level of B2–microglobulin versus 10 months in patients with normal levels of serum B2–microglobulin(P 0.4). Median PFS was 7 months for stage I disease, 6 months for stage II disease and 5 months for stage III disease (P– 0.02). Median PFS in patients with normal serum LDH was 7 months versus 5 months in those with elevated serum LDH (P 0.007).

Median PFS was better in patients with normal calcium level than those presented with hypercalcemia (7 months vs. 4 months) (P 0.009) while it was better in patients with normal serum calcium level than those with elevated serum calcium level (7 months vs. 5 months) (P 0.002).

Discussion

In this study, we tried to explore well–known and evidence–based prognostic factors and their impact on MM patients' response to treatment. Different prognostic factors were correlated with OS and PFS. We found that the female gender was better than males with regards to OS but not to PFS. Females have better OS (39 months vs 14 months) than males (P– 0.025). PFS was 7 months in females versus 6 months in males (P: 0.88).

Regarding performance status, survival of patients with PS I was 39 months while those with PS II was 12 months (P: 0.005) and PSIII was 5 months (P: 0.001). Associated co–morbidities varied from hypertension, IHD, DM, COPD, CVS, renal failure as well as chronic liver disease. OS of patients with no co–morbidity was 27 months versus 9 months for comorbid patients (P: 0.01). OS was better in patients who had <3 bony lesions (P: 0.03) while PFS did not vary significantly (8 months vs. 6 months) (P: 0.08). Survival of those without pathological fracture compared to those with pathological fracture (27 months vs. 19 months) was insignificant (P: 0.11). Patients who have no paraprotein in urine had statistically significant better OS than those who were positive (39 months vs. 18 months) (P 0.04). Patients who have no paraprotein in serum have better OS but were statistically insignificant (P: 0.273)

Patients with good performance status have a median survival of 36 months compared to 11 months for those with performance status of 3–4. [35]

OS for patients with below–normal hemoglobin was 22 months (P: 0.16). PFS was 25 months for patients with normal hemoglobin level versus 6 months for patients with hemoglobin <normal (P: 0.09). OS for patients with hypoalbuminemia (<3.5 gm/dl.) was 19 months (P: 0.006). PFS was 7 months vs. 5 months (P: 0.29). OS for patients with elevated B2–microglobulin was 19 months with (P: 0.02). PFS was insignificantly better in patients with normal levels of serum B2M (10 months vs. 6 months) (P: 0.4). OS in patients with stage II disease was 18 months and it was 12 months for stage III disease (P: 0.001). PFS was 7 months for stage I disease, 6 months for stage II disease and 5 months for stage III disease with significant (P: 0.02).

B2–microglobulin is affected by renal function, MM, age, infections, or other kidney problems, which is why B2–microglobulin abrogates the independent prognostic value of other renal indicators (creatinine,

Studied factor	variant	Response Rate (n, %)	Progression (n, %)	P–Value
Age	< 60 yrs.	27 (56.3%)	21 (43.8%)	0.9
	≥ 60 yrs.	6 (54.5%)	5 (45.5%)	
Gender	Females	16 (66.7%)	8 (33.3%)	0.16
	Males	17 (48.6%)	18 (51.4%	
S. Albumin	> 3.5 gm/dl.	11 (73.3%)	4 (26.7%)	0.11
	≤ 3.5 gm/dl.	22 (50%)	22 (50%)	
B2M	≤ 2 U/mL.	6 (75%)	2 (25%	0.44
	> 2 U/mL.	27 (52.9%)	24 (47.1%)	
International staging system	ISS–I	12 (75%)	4 (25%)	0.05
	ISS–II	17 (56.7%)	13 (43.3%)	
	ISS–III	4 (30.8%)	9 (69.2%)	
Hemoglobin	≥ 12.5 gm%	5 (71.4%)	2 (28.6%)	0.44
	< 12.5 gm%	28 (53.8%)	24 (46.2%)	
Serum LDH	≤ 480 mg/dl.	23 (67.6%)	11 (32.4%	0.035
	> 480 mg/dl.	10 (40%)	15 (60%)	
Plasma cells in BM	≤ 5%	9 (75%)	3 (25%)	0.13
	>5%	24 (51.1%)	23 (49.9%)	
S. Calcium	≤ 11%	28 (57.1%)	21 (42.9%)	0.67
	> 11%	5 (50%)	5 (50%)	
S. Creatinine	≤ 1.4 mg/dl.	31 (63.3%)	18 (36.7%)	0.01
	> 1.4 mg/dl.	2 (20%)	8 (80%)	
Bony lesions	< 3 lesions	10 (71.4%)	4 (28.6%)	0.18
	≥ 3 lesions	23 (51.1%)	22 (48.9%)	

Table 4. Response to first line treatments given for MM patients.

urea, and so forth) in multivariate analyses. B2–microglobulin can also be used as a continuous variable because the higher the B2–microglobulin value, the shorter the survival. [36]

Regarding serum LDH, OS was significantly better in patients with normal LDH (39 vs. 12 months) (P: 0.001). PFS was better in patients with normal LDH (7 vs. 5 months) than those with elevated LDH (P: 0.007). In selected patients treated with combinations of novel agents and tandem transplantation, LDH is an independent prognostic factor and is associated with a short event–free and overall survival even when cytogenetic abnormalities and gene expression signature are considered. [37].

OS was better in patients presented with normal serum calcium level than those presented with hypercalcemia (27 months vs. 10 months) (P: 0.03). PFS was better in patients with normal serum calcium (7 vs. 4 months) than those with elevated serum calcium (P: 0.009). OS for patients with normal creatinine level was 27 versus 13 months for those presented with elevated serum creatinine

FACTOR	MEDIAN PFS	PFS P=VALUE	MEDIAN OVERALL SURVIVAL (OS)	OS P=VALUE
AGE <60 years	6 months	P 0.14	37 months	P = 0.001
AGE >60 years	6 months		12 months	
SEX – Female	7 months	P 0.88	39 months	P = 0.025
SEX – Male	6 months		14 months	
+ Co–morbid disease			9 months	P = 0.01
No co–morbidity			27 months	
PS ECOG I			39 months	P = 0.005
PS ECOG II			12 months	
PS ECOG III			5 months	
Multiple skeletal lesions ≥3	6 months	P 0.08	19 months	P = 0.03
≤3 skeletal lesions	8 months		38 months	
With Pathological fracture			19 months	P = 0.11
Without Pathological fracture			27 months	
With Plasmacytoma			38 months	P = 0.05
Without plasmacytoma			14 months	
Elevated serum paraprotein			18 months	P = 0.27
No paraprotein in serum			39 months	
Non–detected paraprotein in urine	5 months		39 months	P = 0.045
With para proteinuria	7 months		18 months	
Hemoglobin level <12.5 gm/dl	6 months		22 months	P = 0.16
Hemoglobin level ≥12.5 gm/dl	25 months			
With hypoalbuminemia <3.5 gm/dl	7 months	P 0.29	19 months	P = 0.006
Normal albumin	5 months		Not reached	
Elevated B2M	6 months	P 0.4	19 months	P = 0.02
B2M >2 or normal	10 months		Not reached	
Stage I	7 months	P 0.02		
Stage II disease	6 months		18 months	P = 0.001
Stage III disease	5 months		12 months	
Elevated serum LDH	5 months	P 0.007	12 months	P = 0.001
Normal serum LDH	7 months		39 months	

BM Plasma cell percentage <5%	7 months	P 0.4	46 months	P = 0.14
BM plasma cell percentage >5%	6 months		20 months	
Normal serum calcium level	7 months	P 0.009	27 months	P = 0.03
Hypercalcemia	4 months		10 months	
Normal serum creatinine level	7 months	P 0.002	27 months	P = 0.005
Elevated serum creatinine level	5 months		13 months	

Table 5 : Comparison of Median PFS and Median OS.

level (P: 0.005). PFS was better in patients with normal creatinine level than those with elevated serum creatinine level (7 vs. 5 months) (P: 0.002). Creatinine, calcium, albumin, immunoglobulin class subtype, and the extent of the bone–marrow involvement are all significant predictors of survival. [38]

OS for patients with plasma cell % in BM <5% was 46 months versus 20 months for patients with plasma cell % in BM >5% was insignificant (P: 0.14). PFS was better in patients with plasma cell % in BM less than 5% was (7 versus 6 months) in patients with plasma cell % in BM >5% with (P: 0.4). A high number of PCs in BM and a diffuse pattern of infiltration are generally associated with a poor prognosis. [39]

Most of our patients received chemotherapy treatments like VAD as a first line, MP mostly as a second–line treatment. Other treatments given were Thal–Dex., CVP, DCEP, Dex, RTH. We studied the impact of different prognostic factors on the response to treatment in our patients. Among these factors that significantly affected treatment outcomes were serum creatinine (p=0.012) and LDH (p=0.035).

While no specific genetic markers are required in the diagnosis of multiple myeloma (MM), multiple genetic abnormalities and gene signatures are used in disease prognostication and risk stratification. Nowadays, cytogenetic evaluation is mandatory in all patients with newly diagnosed MM and should always include interphase FISH in purified plasma cells or in combination with immunofluorescent detection of light–chain–restricted plasma cells (cIg–FISH). Cytogenetic abnormalities in MM can be classified into 2 main groups: translocations involving the IGH locus and genomic imbalances. Patients can have one or more of these abnormalities and in general, over time, there is an accumulation of new cytogenetic abnormalities. Some cytogenetic abnormalities are unequivocally associated with poor outcomes e.g. (17p deletion)., t(4;14)*, t(14;16), t(14;20). [40]

Conclusion

Based on the results of the study, we can conclude that overall survival (OS) is significantly correlated with age, sex, performance status, comorbidities, presence of ≥3 skeletal lesions, detection of paraprotein in the urine, levels of albumin, calcium, creatinine and serum LDH in the blood. Patients with better survival rates are those who are <60 years old, at PS ECOG I, with no co–morbid diseases, ≤3 skeletal lesions, non–detected paraprotein in the urine, and maintain normal levels of albumin, calcium, creatinine and serum LDH. OS of females is higher compared to males (39 months vs 14 months).

The presence of absence of pathological fracture, plasmacytoma, serum paraprotein, B2M, BM plasma cell percentage, and hemoglobin levels do not significantly affect the OS of patients.

Progression–free survival of MM is interrelated with the stage of the disease and the presence of elevated serum LDH, hypercalcemia and elevated serum creatinine. PFS is not significantly linked with age, sex, performance status, presence of skeletal

lesions, levels of albumin, B2M and BM plasma cell percentage.

References

1. Bida JP, Kyle RA, Therneau TM, Melton LJ 3rd, Plevak MF, Larson DR, et al. Disease associations with monoclonal gammopathy of undetermined significance: a population–based study of 17,398 patients. Mayo Clin Proc. Aug 2009;84(8):685–93. (Medline).(Full Text).
2. Kristinsson SY, Bjorkholm M, Andersson TM, et al. Patterns of survival and causes of death following a diagnosis of monoclonal gammopathy of undetermined significance (MGUS): a population–based study. Haematologica. Jul 16 2009;epub ahead of print. (Medline).(Full Text).
3. P. L. Bergsageland W.M. Kuehl, "Molecular pathogenesis and a consequent classification of multiple myeloma," Journal of Clinical Oncology, vol. 23, no. 26, pp. 6333–6338, 2005.
4. W. J. Chng, O. Glebov, P. L. Bergsagel, and W. M. Kuehl, "Genetic events in the pathogenesis of multiple myeloma, "Best Practice and Research: Clinical Haematology, vol. 20, no. 4, pp. 571–596, 2007.
5. R. Fonseca, E. Blood, M. Rue et al., "Clinical and biologic implications of recurrent genomic aberrations in myeloma," Blood, vol. 101, no. 11, pp. 4569–4575, 2003.
6. R. Fonseca, P. L. Bergsagel, J. Drach et al., "International myeloma working group molecular classification of multiple myeloma: spotlight review," Leukemia, vol. 23, no. 12, pp.2210–2221, 2009.
7. F. Zhan, Y. Huang, S. Colla et al., "The molecular classification of multiple myeloma," Blood, vol. 108, no. 6, pp. 2020–2028, 2006.
8. J. D. Shaughnessy, F. Zhan, B. E. Burington et al., "A validated gene expression model of high–risk multiple myeloma is defined by deregulated expression of genes mapping to chromosome 1," Blood, vol. 109, no. 6, pp. 2276–2284, 2007.
9. J. San–Miguel, M. V. Mateos, and N. C. Gutierrez, "Risk stratification in the era of novel therapies," Cancer Journal, vol. 15, no. 6, pp. 457–464, 2009.
10. N. V. Smadja, C. Fruchart, F. Isnard et al., "Chromosomal analysis in multiple myeloma: cytogenetic evidence of two different diseases," Leukemia, vol. 12, no. 6, pp. 960–969, 1998.
11. C. S. Debes–Marun, G. W. Dewald, S. Bryant et al., "Chromosome abnormalities clustering and its implications for pathogenesis and prognosis in myeloma," Leukemia, vol. 17, no. 2, pp. 427–436, 2003.
12. R. Fonseca, C. S. Debes–Marun, E. B. Picken et al., "The recurrent IgH translocations are highly associated with non–hyperdiploid variant multiple myeloma," Blood, vol. 102, no.7, pp. 2562–2567, 2003.
13. H. Avet–Loiseau, M. Attal, P. Moreau et al., "Genetic abnormalities and survival in multiple myeloma: the experience of the Intergroupe Francophone du My´elome," Blood, vol. 109,no. 8, pp. 3489–3495, 2007.
14. S. K. Kumar, J. R. Mikhael, F. K. Buadi et al., "Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk–Adapted Therapy (mSMART) consensus guidelines," Mayo Clinic Proceedings, vol. 84, no. 12, pp. 1095–1110, 2009.
15. D. R. Carrasco, G. Tonon, Y. Huang et al., "High–resolution genomic profiles define distinct clinico–pathogenetic subgroups of multiple myeloma patients," Cancer Cell, vol. 9, no.4, pp. 313–325, 2006.
16. M. Chesi, E. Nardini, R. S. C. Lim, K. D. Smith, W. Michael Kuehl, and P. L. Bergsagel, "The t(4;14) translocation in myeloma dysregulates both FGFR3 and a novel gene, MMSET, resulting in IgH/MMSET hybrid transcripts," Blood, vol. 92, no. 9, pp. 3025–3034, 1998.
17. J. J. Keats, T. Reiman, C. A. Maxwell et al., "In multiple myeloma, t(4;14)(p16;q32) is an adverse prognostic factor irrespective of FGFR3 expression," Blood, vol. 101, no. 4, pp. 1520–1529, 2003.
18. H. Avet–Loiseau, J. Soulier, J. P. Fermand et al., "Impact of high–risk cytogenetics and prior therapy on outcomes in patients with advanced relapsed or refractory multiple myeloma treated with lenalidomide plus dexam´ethasone," Leukemia, vol. 24, no. 3, pp. 623–628, 2010.
19. M. Mateos, N. Gutierrez, and B. Paiva, "Clinical outcome according to both cytogenetic abnormalities (CA) detected by fluorescence in situ hibridization (FISH) and hyperdiploidy assessed by flow cytometry (FCM) in elderly newly diagnosed myeloma patients treated with A Bortezomib–based combination," Blood, 2010, abstract 309.
20. J. F. SanMiguel, R. Schlag, N. K. Khuageva et al., "Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma," The New England Journal of Medicine, vol.359, no. 9, pp. 906–917, 2008.
21. H. Avet–Loiseau, F. Malard, L. Campion et al., "Translocation t(14;16) and multiple myeloma: is it really an independent prognostic factor?" Blood, vol. 117, no. 6, pp. 2009–2011, 2011.
22. J. D. Hoyer, C. A. Hanson, R. Fonseca, P. R. Greipp, G. W.Dewald, and P. J. Kurtin, "The (11;14)(q13;q32) translocation in multiple myeloma: a morphologic and immunohistochemical study," American Journal of Clinical Pathology, vol. 113, no. 6, pp. 831–837, 2000.
23. R. Garand, H. Avet–Loiseau, F. Accard, P. Moreau, J. L. Harousseau, and R. Bataille, "t(11;14) and t(4;14) translocations correlated with mature lymphoplasmacytoid and immature morphology, respectively, in multiple myeloma," Leukemia, vol. 17, no. 10, pp. 2032–2035, 2003.

24. R. Fonseca, E. A. Blood, M. M. Oken et al., “Myeloma and the t(11;14)(q13;q32); evidence for a biologically defined unique subset of patients,” Blood, vol. 99, no. 10, pp. 3735–3741, 2002

25. W. J. Chng, S. Kumar, S. Van Wier et al., “Molecular dissection of hyperdiploid multiple myeloma by gene expression profiling” Cancer Research, vol. 67, no. 7, pp. 2982–2989, 2007.

26. K. Anderson, C. Lutz, F. W. van Delft et al., “Genetic variegation of clonal architecture and propagating cells in leukemia,” Nature, vol. 469, no. 7330, pp. 356–361, 2011.J. Drach, J. Ackermann, E. Fritz et al., “Presence of a p53 gene deletion in patients with multiple myeloma predicts for short survival after conventional–dose chemotherapy,” Blood, vol.92, no. 3, pp. 802–809, 1998.

27. F. Zhan, S. Colla, X. Wu et al., “CKS1B, overexpressed in aggressive disease, regulates multiple myeloma growth and survival through SKP2– and p27Kip1–dependent and – independent mechanisms,” Blood, vol. 109, no. 11, pp. 4995–5001, 2007.

28. G. Tricot, B. Barlogie, S. Jagannath et al., “Poor prognosis in multiple myeloma is associated only with partial or complete deletions of chromosome 13 or abnormalities involving 11q and not with other karyotype abnormalities,” Blood, vol. 86, no. 11, pp. 4250–4256, 1995.

29. W. J. Chng, R. Santana–D´avila, S. A. vanWier et al., “Prognostic factors for hyperdiploid–myeloma: effects of chromosome 13 deletions and IgH translocations,” Leukemia, vol. 20, no. 5,pp. 807–813, 2006.

30. N. C. Guti´errez, M. V. Castellanos, M. L. Mart´ın et al., “Prognostic and biological implications of genetic abnormalities in multiplemyeloma undergoing autologous stem cell transplantation: t(4;14) is the most relevant adverse prognostic factor, whereas RB deletion as a unique abnormality is not associated with adverse prognosis,” Leukemia, vol. 21, no. 1, pp. 143–150,2007.

31. L. Chiecchio, R. K. M. Protheroe, A. H. Ibrahim et al., “Deletion of chromosome 13 detected by conventional cytogenetics is a critical prognostic factor in myeloma,” Leukemia, vol. 20, no. 9, pp. 1610–1617, 2006.

32. P. L. Bergsagel, W. M. Kuehl, F. Zhan, J. Sawyer, B. Barlogie, and J. Shaughnessy, “Cyclin D dysregulation: an early and unifying pathogenic event in multiple myeloma,” Blood, vol. 106, no. 1, pp. 296–303, 2005.

33. W. J. Chng, E. Braggio, G. Mulligan et al., “The centrosome index is a powerful prognostic marker in myeloma and identifies a cohort of patients that might benefit from aurora kinase inhibition,” Blood, vol. 111, no. 3, pp. 1603–1609, 2008.

34. R. Fonseca and J. San Miguel, “Prognostic factors and staging in multiple myeloma,” Hematology/Oncology Clinics of North America,2009

35. Rajkumar S. Vincent & Francis Buadi: Best Practice & Research Clinical Haematology Vol. 20, No. 4, pp. 665–680, 2007.

36. Rafael Fonseca, Jesus San Miguel, Prognostic Factors and Staging in Multiple Myeloma HematolOncolClin N Am 21 (2007) 1115–1140

37. Bart Barlogie and John Crowley Could CR mean cure, by The American Society of Hematology, 2011.

38. Kyle RA. Prognostic factors in multiple myeloma. Stem Cells ,(1995; 2: 56–63.)

39. Rafael Fonseca, Jesus San Miguel, Prognostic Factors and Staging in Multiple Myeloma HematolOncolClin N Am 21 (2007) 1115–1140

40. P. Leif Bergsagel,1 María–Victoria Mateos, et.al, Improving overall survival and overcoming adverse prognosis in the treatment of cytogenetically high–risk multiple myeloma, The American Society of Hematology, Blood Journal, 2013.