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Original Article

Real World Multiple Myeloma Registry from Jordan, a Developing Country

Farah Qasem[1], A'sem Abu-Qamar[1], Batool Aqel[1], Rand Aladayleh[1], Ilham Alteerah R.[1], Ahmad Magableh[4], Hisham Bawa" neh[4], Feras Al-fararjeh[1,2] and Abdalla Awidi[1,2,3].

[1] Medical school, The University of Jordan, Amman, Jordan.
[2] Jordan University Hospital, Amman, Jordan.
[3] Cell Therapy Center, The University of Jordan, Amman, Jordan.
[4] Al-Basheer Hospital, Ministry of Health, Amman, Jordan.

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Abstract. ***Background and objective:*** **Scanty reports from the middle east and north Africa (MENA) region have been published on multiple myeloma (MM). Multiple myeloma registry has been established at Jordan University Hospital (JUH) since 2009. Our work aims to review this Multiple Myeloma registry with data from 113 patients diagnosed with MM at JUH and analyze their management and course.**
Methods: **This is a non-interventional and retrospective analysis of the MM registry from 2009-to 2016 involving 113 patients at JUH. Statistical analysis was done using the Statistical Package for the Social Sciences (SPSS). Overall survival (OS) was analyzed with the Kaplan-Meier method. P-value was considered significant if it was (<0.05).**
Results: **We found no gender difference in this registry. The median age is 62 years. Most patients are in ISS stage II and III (36.28% for each). Immunoglobulin type G Kappa is the dominant subtype. Bone pain is the most common presenting symptom. The most common laboratory finding is anemia (45.6%). Most of our patients (85.2%) had received thalidomide and dexamethasone, while only 14.8% received bortezomib, thalidomide, and dexamethasone.**
Our patients' mean overall survival (OS) was 74 months, and the median survival was 38 months. For ISS stages I, II, and III, median OS was 96, 46, and 16 months.
Conclusion: **MM in a developing country presents a challenging disease compared to industrial countries in both epidemiology and management. An improved road map in the care of MM in these countries is needed. The use of three or four drugs combination upfront is warranted. However, this is limited because of the high cost of these drugs. We expect the following decade to show better survival and quality of life for MM patients once these drugs are widely used.**

Keywords: Multiple myeloma; Survival; Treatment; Thalidomide; Bortezomib.

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Correspondence to: Abdalla Awidi. Cell Therapy Center, The University of Jordan, Queen Rania str, Jubaiha, Amman 1194, Jordan. Tel.: +9626535000. E-mail: aabbadi@ju.edu.jo, Abdalla.awidi@gmail.com

Introduction. Multiple myeloma accounts for 13-15% of all hematological malignancies, the second most common after non-Hodgkin lymphoma.[1] It is usually a disease of older people, and its incidence is variable by geographic area, being most common in developed countries where the incidence is increasing with age.

USA data show that it is more frequent in males and black people.[2] In industrial countries, the median patient's age at diagnosis is approximately 66–70 years old, with 37% of patients younger than 65 years of age.[1] Symptomatic multiple myeloma is associated with significant morbidity and mortality, especially with end-organ failure.[3]

There have been significant improvements in treating multiple myeloma in the last few years. The introduction of autologous hematopoietic stem cell transplantation has positively impacted overall survival. In addition, novel agents such as proteasome inhibitors, immunomodulatory drugs, monoclonal antibodies, and CAR-T cells are changing the history of the disease, producing higher progression-free survival and overall survival.[4]However, these new drugs are very expensive, and a cost/benefit balance is advisable[5]

Few studies have been published from developing countries describing the epidemiology of the disease,[6- 8] with very scanty reports from the middle east and north Africa (MENA) region.[9-12]

Since the population in the MENA region is expected to have a more aging population in the coming decades, the incidence is expected to increase, as shown in a recent publication from Lebanon.[12] We are not aware of any published work on a large cohort of patients with multiple myeloma from Jordan.

The aim of this study is to review the department registry of multiple myeloma patients at Jordan University Hospital (JUH), which is representative of the whole country, over eight years with patient characteristics and disease patterns, survival, and therapy used in a real-world experience.

Methods. Patients. This non-interventional, single-center, retrospective study analyzes the registry of patients with newly diagnosed multiple myeloma (MM) between 01/2009 and the end of 2016.

A total of 128 patients were reviewed, representing (27.6%) of all MM patients in the country during the study period, estimated to be around 464 patients as reported by the Jordanian National cancer registry.[13] The registry captures data prospectively. The data include patients' particulars, medical history, and diagnostic tests, including imaging tests, stage, pathology, laboratory findings, follow-up, therapy, and cytogenetics. As for the imaging tests, an x-ray of the skull and skeletal survey of the long bones and spine were done. In selected patients and in those not showing abnormal findings on x-ray images, MRI images of the spine or the suspected affected area were done. In some patients, PET scans were carried out. No patient had a low dose whole body ct scan.

Patients who entered the registry between the beginning of 2009 and the end of 2016 are the subject of this report.

This study was approved by the Institutional Review Board committee of the Cell Therapy Center and JUH, Amman, Jordan. Written informed consent that adhered to the declaration of Helsinki was obtained from all participants. The patient must be 18 years old or older.

Diagnosis of multiple myeloma, staging, and risk classification were made in accordance with ESMO guidelines.[14]

As for the treatment, only two different reimbursable regiments were used as first-line; a combination of dexamethasone and thalidomide (DT), which was dominantly used in the first few years of the registry, and a combination of Bortezomib (Velcade), dexamethasone and thalidomide (VDT) which was used during the later years of the registry or for patients considered candidates for single autologous bone marrow transplantation (ABMT) with high dose melphalan (180mg/m^2). If the patient progressed or failed first-line therapy, the reimbursed drugs were dexamethasone with melphalan or drug alone with or without palliative radiation. Subjects who had autologous bone marrow transplantation were given monthly bortezomib post-ABMT maintenance for one year. If they relapse, there was no specific reimbursable combination. Renal insufficiency was defined as per ESMO guidelines in the CRAB criteria (serum creatinine >177mol/L (>2mg/dL).

The Statistical analysis was done using the Statistical Package for the Social Sciences (SPSS). Overall survival (OS) was analyzed with the Kaplan-Meier method. P-value was considered significant if it was <0.05.

Results. One hundred twenty-eight patients with MM were diagnosed and treated between 2009 and 2016 at JUH. Demographic and laboratory data are shown in **table 1**. The mean age was 63.3 years. Again, the distribution of ages was found to be equal in both genders, with 50% of each gender. Regarding the presenting symptomatology and findings, 61.1% complained of bone pain, with 70.5% of patients having lytic bone lesions on x-ray imaging or MRI imaging, 45.6% had symptoms of anemia, and 20% had renal insufficiency as defined by ESMO guidelines (serum creatinine > 177 µmol/L (> 2 mg/dL). Concerning the immunoglobulin subtypes of multiple myeloma in the entire population, 79.1% of the patients had the IgG monoclonal band, of which 79.2% had IgG Kappa myeloma, and 20.8% had IgG lambda myeloma 13.9% of the patients had the IgA monoclonal band, of which 56.25% had IgA kappa myeloma, and 43.75% had IgA lambda myeloma. In addition, 7% of the patients had light chain myeloma. As for the ISS stage, 27.4% were stage I, 36.28% were stage II, and 36.28 were stage III. The mean and median survival for each type is shown in **table 2**. Survival analysis of the non-transplant population (113) patients was as follows: Median overall survival (95%

Table 1. Demographic and laboratory data of all the patients with multiple myeloma.

Gender	**Percentage**
Male	64 (50%)
Female	64 (50%)
Age groups	
< 65	75 (58.6%)
≥ 65	53 (41.4%)
Mean	61.3
Median	55.3
Duration of follow up	
Mean follow up (months)	36.8 ± 3.44
Median follow up (months)	32
Presenting symptomatology*	
Lytic lesions	73.5%
Bone pain	64.1%
Anemia	48.6%
Renal insufficiency +	19%
Hypercalcemia	12.6%
Bleeding	6.6%
Others	7.6%
ISS score at diagnosis**	
Stage I	31 (24.2%)
Stage II	44 (34.38%)
Stage III	53 (41.4%)
Disease characteristics by Immunoglobulin electrophoresis:	
IgG	79.7%
IgG Kappa	79.2%
IgG Lambda	20.8%
IgA	12.5%
IgA Kappa	56.25%
IgA Lambda	43.75%
Light chain	7.8%
Treatment ++: DT VTD	75% 25 %

* Some of the symptoms may overlap. DT Dexamethasone and thalidomide. VDT: Bortezomib (Velcade), Dexa and Thalidomide. ** as per ESMO guidelines. + serum creatinine > 177 μmol/L (> 2 mg/dL). ++ this treatment applies to non-transplant population. For abmt population, see text.

confidence interval [CI]) was 38.00 months (Range: 23.133-52.867). Stage 1 had a median survival of 96 months. Stage II had a median survival of 46. months and stage III had a median survival of 16. months (**Table 2**). **Figure 1** demonstrates the survival difference between the ISS stage and the different immunoglobulin types of myelomas. There was a statistical significance concerning ISS stages ($p < 0.05$). However, the survival difference between the types of myelomas was statistically insignificant ($p>0.05$), as shown in **table 2**. 85.2% of the patients were treated using DT, while 14.8% were treated using VDT (**Table 2**). **Figure 2** demonstrates the survival difference between treatment regimens used. The survival analysis was not statistically significant ($p > 0.05$) (**Table 2).** Survival curves are shown in **figures 1 and 2**. As for the overall survival (OS) and progression-free survival (PFS) in the ABMT population, details are shown in **figure 2.**

Discussion. Our study involves 128 Multiple Myeloma patients who were followed at the Hematology department of JUH and was the first conducted in Jordan.

The yearly number of new myeloma cases in Jordan was 58 cases per year during the registry period.[13] During the period 2009 to 2016, it is estimated that 464 new cases were diagnosed with myeloma in the whole

Table 2. Mean and Median for Survival Time in months as per ISS stage, type of paraprotein and therapy.

ISS	Mean				Median	
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error
			Lower Bound	Upper Bound		
Stage I	112.260	17.597	77.769	146.751	96.000	26.354
Stage II	78.179	13.288	52.134	104.224	46.000	18.990
stage III	30.291	7.586	15.422	45.160	16.000	4.210
Overall	74.169	8.864	56.795	91.543	38.000	7.585
Treatment						
DT	95.144	16.657	62.496	127.792	107.000	18.788
DT	66.748	9.321	48.480	85.017	38.000	2.832
Overall	72.557	8.620	55.662	89.451	41.000	8.123
Types						
IgG	63.992	8.606	47.124	80.859	36.000	4.234
IgA	55.882	15.225	26.041	85.723	33.000	7.318
Overall	63.969	7.721	48.836	79.102	36.000	1.927

DT: Dexamethasone and Thalidomide. VTD: Bortezomib (velcade), Dexamethasone and thalidomide.

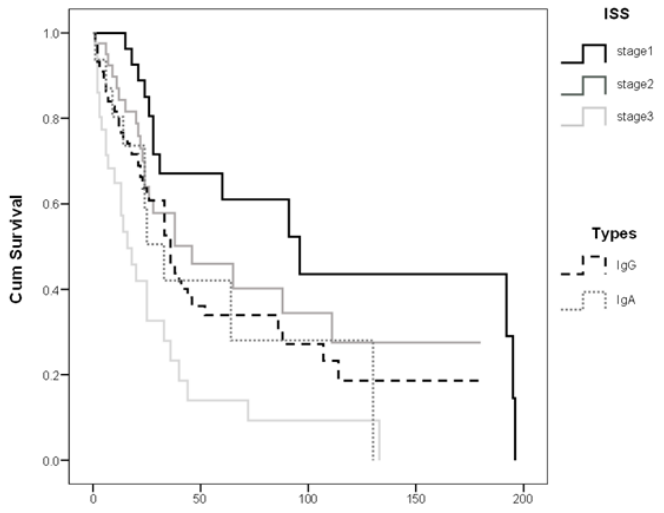

Figure 1. Survival as per stage and the abnormal IgG and IgA paraprotein detected.

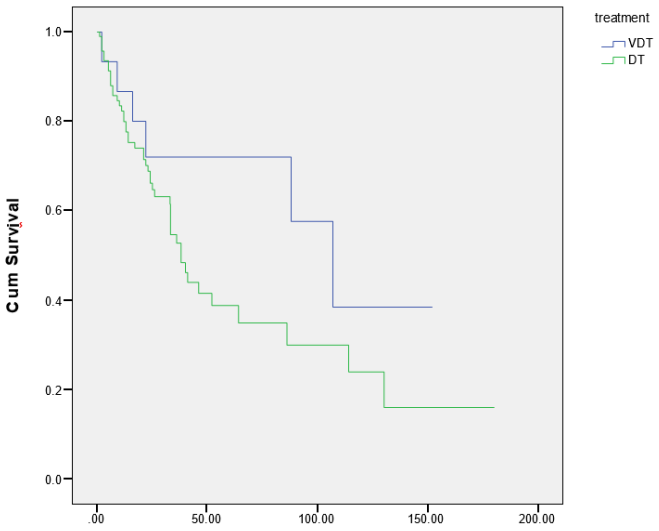

Figure 2. Survival (months) as per drug combination used.

country. With 128 cases in our registry during the same period, it seems that it captured (27.6%) of all myeloma cases in Jordan, which makes it very representative of the disease in the country. There was no difference in gender distribution, as found in the Jordan cancer registry in 2012.[13] The gender distribution is similar to that reported from Latin America[5] but was significantly different from Iran.[8]

The median age of our patients was 55.3, and the mean age ± SD was 61.30±10.8, which is comparable to the Iranian study's mean age± SD of 61.98±11.44 years. [8] Other studies from the MENA region showed an even younger median age, such as the study from Algeria that showed a median age of 53 years.[10] The age of our patients is not close to the age of 66 years reported by the Mayo clinic series.[15]

We found out that 58.6% of our patients were younger than 65 years, comparable to the Iranian study. In contrast, a Swedish study showed that 72% of their patients were older than 65 years.[16] In a real-world study conducted in Europe, the Middle East, and Africa, 75% of patients were older than 65.[17]

The most common presenting symptom in our patients was bone pain (61.1%), similarly to the studies from Belgium, France, Germany, Italy, Spain, Switzerland, and the UK,[18] as well as the study reported from Beijing/China.[19] However, the registry did not capture skeletal-related events (SRE) in the disease course other than at presentation.

The prevalence of anemia during the disease is about 45.2% in our study, which is close to the prevalence reported in a recent registry study in the USA (45%).[20] The Swedish study showed a comparable percentage of patients with anemia (49%).[16]

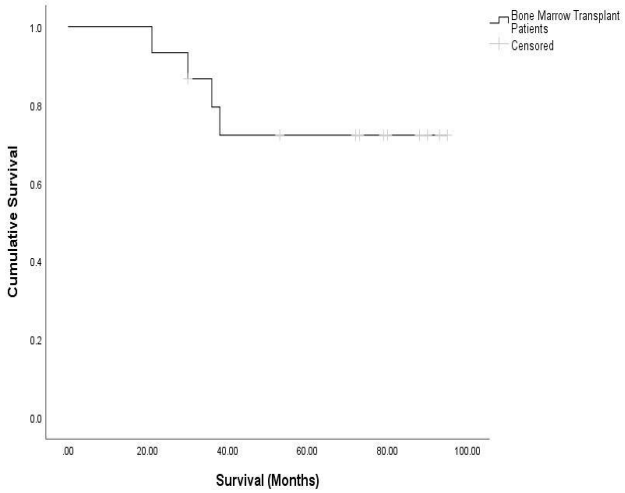

Figure 3. OS patients with aBMT.

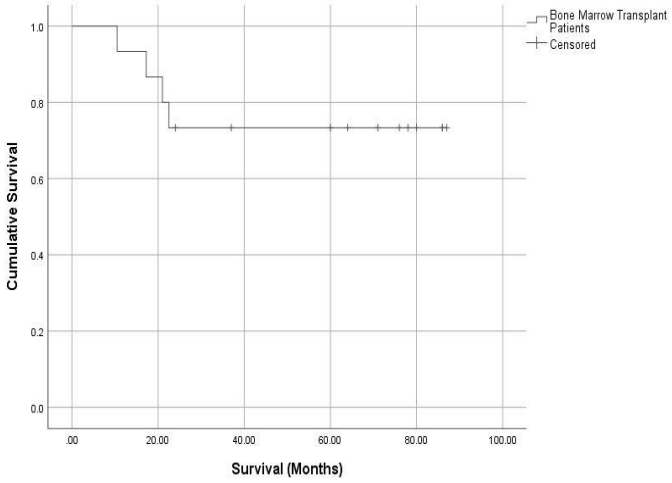

Figure 4. PFS of aBMT patients.

The prevalence of renal dysfunction as defined by ESMO guidelines in our study was 20%, similar to that reported in European countries (20%)[17] and in the Swedish study (18%).[16] The Iran study reported that 33.8% of their patients had a creatinine higher than 2.[8]

Hypercalcemia was seen in 11.6% of our patients, similar to that reported in the Mayo clinic[15] and the Swedish studies,[16] 13% in both. Hypercalcemia was slightly higher in the European countries study, which was reported in 19% of patients.[18]

73.5% of our patients had osteolytic lesions by imaging (shown in **table 1**), comparable to the Swedish study (77%).[16]

Figures 3 and 4 show the mean overall survival (OS) and progression-free survival in transplant patients, which was not reached during the follow-up period.

We noticed certain important findings when comparing survival results in this study with other reported studies.[21-26]

For ISS stages I, II, and III, median OS were 96, 46, and 16 months, respectively. Comparing this with the RS (rescaled range) in the Swedish study, it shows a similar median survival for ISS stage I, which was 8.2 years, and lower median survival for stage II and III; 5.6 and 3.2 years, respectively.[16]

Since most of our patients represent a typical Jordanian population in which most people are working class, lower and middle-income class, it may be possible that the poor outcome might be explained, in part, by the poor economic status of these patients. Socioeconomic status is reported to be a prognostic factor for the overall survival of multiple myeloma patients, as shown in recent publications.[27] In the Middle East and North Africa, extreme poverty rates nearly doubled between 2015 and 2018, from 3.8% to 7.2%, according to the world bank report 2020.[28]

Based on new data, on July 1, 2017, the World Bank classified Jordan as a lower-middle-income country.[29] Given all these socioeconomic factors in the middle east, it is only expected to find lower survival related to multiple myeloma compared to European or industrial countries.

Since most Jordanians are ethnic Arabs, the ethnicity probably does not play a role in our study despite being reported in other countries to be of importance.[30] Most of our patients at the time of diagnosis had ISS stage II (34.38%) and stage III (41.4%), and only 24.2% with stage I. The fact that the patients present in the advanced stage indicates a lack of proper awareness and patient education.

A study from South Korea reported that 48.8% of Multiple Myeloma patients were ISS stage II and 40.2% were ISS stage III, while only 11% were stage I.[31] In the Swedish study, 44% of the patients were reported to be at ISS stage II at diagnosis and 33% at stage III.[16] These findings suggest that patients in Jordan and internationally have significant MM-related organ damage at diagnosis, so initiatives facilitating earlier diagnosis are warranted.

VDT (Bortezomib, Dexamethasone, Thalidomide) was used in 14.8% of our patients, DT (Dexamethasone and Thalidomide) in 85.2%. The mean survival time for each regimen was: 95 and 66 months, respectively. Unfortunately, our institution at the time of the study did not have the approval to reimburse bortezomib until late in the registry; hence VDT was not widely used. In addition, we had no access to second-line new drugs for the treatment of MM.

As for the types of proteins secreted by the malignant plasma cells, the most common type was IgG (79.1%), of which 79.2% had IgG Kappa myeloma, and 20.8% had IgG lambda myeloma. 13.9% of our patients had IgA with equal IgA Kappa and Lambda distribution. Only a small number of patients (7%) had light-chain myeloma. In the Mayo Clinic study, the immunoglobulin distribution for IgG, IgA, and light chain were 52%, 21%, and 16%, respectively.[32]

In our study, the mean survival time for IgG, IgA, and light chain myeloma was 64 months, 56 months, and 34 months. Mean survival for myeloma Lambda light

chains (for IgA and IgG combined) was 73 months, while for Kappa light chains (for IgA and IgG combined) was 58 months.

We believe that reporting our findings will help revisit the management pathways of multiple myeloma in a developing country with limited financial resources. We realize the lack of cytogenetic and molecular data because of non-availability at our institution. Since 2016, we have access to cytogenetics and more recent access to newer agents such as ad lenalidomide, carfilzomib, and daratumumab. However, we still have no access to CAR-T cells.

We need to bridge gaps with institutions in the industrial world to help the patients with mm. Therefore, we welcome establishing more organized collaboration and participation in clinical trials and studies with these institutions.

We believe the decade from 2017 to 2027 will show far better molecular, cytogenetic data and better survival rates.

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