Multiple myeloma in Saudi Arabia: a comprehensive literature review

Fahad Zamel AlSharif

ABSTRACT

Multiple myeloma (MM) accounts for around 1%-2% of all cancers, and it is more prevalent in men than women. MM is responsible for an estimated 176,000 cases and 117,000 deaths annually worldwide. Most myeloma malignancies contain genetic abnormalities that may be identified using sensitive molecular genetic methods such as interphase fluorescence in situ hybridization. The risk categorization has a high prognostic value and aids in the choice of initial treatment options. Diagnostic delays have been linked to worsening the disease’s course and can lead to complications, including pathological fractures and renal failure. They are also connected with worse cancer stages and lower survival rates. There is a scarcity of published data in Saudi Arabia on the characteristics, management practices, as well as outcomes of MM patients. This review discusses the current trends and practices in MM worldwide and compares them with current Saudi Arabia practices.

Keywords: Multiple myeloma, genetic abnormalities, fluorescence in situ hybridization, risk categorization, diagnosis, worldwide, Saudi Arabia.

Introduction

The neoplastic growth of plasma cells generating monoclonal immunoglobulin is a hallmark of multiple myeloma (MM). The plasma cells multiply in the bone marrow (BM), causing osteolytic lesions, osteopenia, and/or pathologic fractures. MM is an uncommon malignancy that accounts for around 1%-2% of all cancers and somewhat more than 17% of hematologic malignancies, and it is more prevalent in men than in women [1].

MM is responsible for an estimated 176,000 cases and 117,000 deaths annually worldwide [2]. MM is primarily a disease of the elderly. Worldwide, the median age at the time of diagnosis ranges between 65 and 74 years, with 10% and 2% of individuals under 50 and 40 years old, respectively [3].

Men are more likely than women to get MM [4]. MM affects people of all ethnicities; however, previous literature has documented that the incidence in African Americans and Black populations is two to three times that of White people [5]; the incidence of MM in Asia is lower [6].

According to a study from the Saudi Cancer Registry, MM accounts for 1% of all cancers and 5% of hematologic malignancies [7]. According to the World Health Organization (WHO) national profile, a percent of 9.6%-11% of cancer-related fatalities in Saudi Arabia were attributable to MM and lymphomas. A recent retrospective study showed that MM Saudi patients are younger, in worse functioning status, and have more advanced stages of the disease, according to the International Staging System (ISS).

Previous literature has hypothesized that Saudi Arabian MM patients are probably more likely to respond to treatment regimens [8]. However, there is a scarcity of published data in Saudi Arabia on the demographic data, modalities of care, and consequences of MM patients. The current review discusses the current trends and practices in terms of MM worldwide and compares them with current Saudi Arabia practices.

Clinical presentation, diagnosis, and diagnostic criteria of MM

One (or more) of the following clinical manifestations frequently leads to the suspicion of MM:
1. Detecting lytic lesions associated with bone pain on regular skeletal films or other imaging techniques.

2. Detecting a monoclonal (M) protein in the serum or urine of patients +/- an elevated concentration of total serum protein.

3. Systemic manifestations suggesting malignancy (i.e., unexplained anemia).

4. Hypercalcemia, either symptomatic or unnoticed.

5. Acute renal failure or, in rare cases, nephrotic syndrome owing to primary amyloidosis.

Most individuals with MM have clinical manifestations due to plasma cell infiltration into the bone or other organs or kidney injury caused by immunoglobulin deposition. Patients present with subacute symptoms, while some individuals have acute symptoms that need immediate attention and care (spinal cord compression, kidney failure, and hyperviscosity). Myeloma-defining events are usually calcium elevation, renal insufficiency, anemia, and bone disease. Pleural effusion and diffuse lung involvement as a result of plasma cell infiltration are uncommon and generally only occur in late disease stages. Individuals are diagnosed earlier in the disease course as "routine" blood testing has become more prevalent [9].

An elevated total serum protein level, most commonly combined with other clinical manifestations suggestive of MM, is often used to diagnose MM. However, in individuals with MM, the total blood protein level may be normal; this is true in light chain MM, where the free light chains (FLC) seldom reach a level that impacts the total protein. Patients with κ light chain were reported to have a higher chance of survival than those with λ light chain disease. Extramedullary plasmacytomas (EP) are seen in around 7% of MM patients at diagnosis and are best identified using imaging scans. EP detected at the time of diagnosis is linked to a worse survival rate. Later while the disease progress, 6% of individuals with MM will develop EP [10]. EP might appear as large, purple lumps under the skin. Plane xanthomas might be a paraneoplastic condition. Cutaneous spicules containing a portion of the monoclonal (M) protein are uncommon [11].

In Saudi Arabia, the International Myeloma Working Group (IMWG) criteria [12] are used to diagnose MM, and the ISS is used to stage MM. A previous study conducted in Saudi Arabia showed that Immunoglobulin (IgG kappa was the most prevalent Ig subtype, followed by light chain (47.6% and 19%) [7]. By using fluorescence in situ hybridization (FISH), approximately half of the 87 patients with cytogenetic analysis data had normal cytogenetics. Deletion 13 was the most prevalent genetic defect (18.4%), followed by Trisomy in 9 patients (10.3%) and t (11,14) in 8 patients (9.2%).

Another study, including 36 Saudi patients, showed that κ chain restriction was reported in 15 females (78.9%), and λ light-chain restriction was reported in 14 males (82.3%). The included patients had higher monocyte percentages, red cell distribution width as well as lower hemoglobin levels. IgG paraprotein and IgA paraprotein were observed in 33 patients (91.7%) and 3 patients (8.3%), while none of the included patients had IgM or IgD paraprotein.

Diabetes mellitus, chronic kidney disease, frequent chest infections, and hypertension were detected in 34 patients (94.4%), 13 patients (36.1%), nine patients (25%), and eight patients (22.2%), respectively [13]. The majority of the Saudi patients (47.5%) had advanced ISS stage III; this is most likely due to delays in diagnosis and referral, while 44 patients (27.8%) and 39 patients (24.7%) had ISS stage I and ISS stage II, respectively [7].

End-organ damage (EOD) is highlighted in the IMWG criteria for diagnosing MM [14]. The diagnosis of MM requires fulfillment of the following criterion:

- Clonal plasma cells in the BM are ≥10% or a biopsy-proven bony or soft tissue plasmacytoma

Plus, one of the following criteria:

- The plasma cell proliferative dysfunction has caused an impairment to organs or tissues (e.g., lytic bone lesions, elevated calcium, renal insufficiency, and anemia)

- A biomarker linked to the almost unavoidable development of EOD (i.e., ≥60 presence of clonal plasma cells within the BM; ≥100 involved/uninvolved FLC ratio (the level of the involved FLC should be ≥100 mg/l); or magnetic resonance imaging (MRI) shows multiple focal lesions.

**Evaluation of suspected cases**

Initial screening procedures for individuals with suspected MM or associated disorders include serum protein electrophoresis with immunofixation as well as a serum FLC assay [15]. The diagnosis of MM is confirmed by performing a BM aspiration and biopsy, radiography, a complete blood count (CBC) with differential, and a chemical screen. To measure the monoclonal and total urine protein concentrations, a 24-hour urine sample for electrophoresis and immunofixation is required [16]. Infiltrated BM with malignant plasma cells might be localized, necessitating several aspirations/biopsies. In order to detect disease location, MRI and/or PET scans can be used [17,18]. Figure 1 depicts the standard diagnostic tests for patients with MM in Saudi Arabia in comparison to the National Comprehensive Cancer Network (NCCN) clinical practice recommendations [19].

The standard imaging method for evaluating myeloma bone disease is still a conventional skeletal survey (CSS). Previous studies documented that CSS has limited sensitivity for detecting myeloma lesions [20]. Modalities used for cross-sectional imaging [i.e., computed tomography (CT) and MRI] have been added to the updated IMWG [14]. A positive CSS is frequent enough...
to rule out serious bone disease and avoid additional imaging, while CT imaging will show significant bone damage in almost 25% of individuals with a negative CSS [20]. A previous consensus documented that, in Saudi Arabia, the imaging methods used include whole-body MRI as well as low-dose CT scans [21].

**Risk stratification**

The results of FISH for certain translocations and other testing are used to risk-stratify individual patients. This risk categorization has a high prognostic value and aids in the choice of initial treatment options. Individuals with high-risk myeloma have a lactate dehydrogenase (LDH) level that is more than two times the institution’s upper range of normal, as well as FISH results showing t(4;14), t(14;16), t(14;20), del17p13, or gain1q, and signs of primary plasma cell leukemia. Standard-risk myeloma is identified in patients who do not exhibit any of the high-risk chromosomal abnormalities or other characteristics. This group includes patients with trisomies like t(11;14) and t(6;14) [14,22,23].

**Intervals to diagnosis**

A previous meta-analysis [24] was conducted to evaluate how long each stage of the diagnostic process took for MM patients, from symptom start to diagnosis confirmation. The authors documented that MM patients wait an average of one month before seeking treatment, with one-quarter of patients waiting more than 3 months. The median duration to diagnosis is 108.6 days (interquartile range = 33.3-241.7), with one-quarter of patients waiting more than 8 months. There were no studies that recorded the time between referral and diagnosis. The average duration until the diagnosis of MM has been established ranges between 3 and 5.5 months, as reported by Surveillance, Epidemiology and End Results-based studies [25]. Another retrospective study documented that diagnosing MM can take more than a year [26]. Diagnostic delays have been linked to worsening the disease’s course and can lead to complications, including pathological fractures and renal failure. They are also connected with worse cancer stages and lower survival rates [27]. No credible data are available to determine the average duration from the first symptoms until a confirmed MM diagnosis.

**Management**

**Induction therapy**

Patients with MM must have an initial examination to assess the extent and locations of MM, as well as the patient’s performance level and any concomitant disorders that might complicate overall care. Furthermore,
specific tests are carried out to evaluate risk stratification
and suitability for autologous stem cell transplantation
(ASCT). In older MM patients, a complete geriatric
assessment may benefit in determining comorbidities and
functional levels, allowing the development of a suitable,
customized management strategy [23].

The vincristine-doxorubicin-dexamethasone (VAD)
regimen is no longer regarded as a preferable induction
regimen in MM since the development of innovative
medications and their shown effectiveness and
tolerance. The usefulness of upfront ASCT has been
debatable in some subgroups during the last decade,
with the introduction of innovative medicines like
immunomodulatory agents, proteasome inhibitors,
and monoclonal antibodies; yet, it is still frequently
recommended for eligible individuals [28].

There is no consensus on the best induction protocol,
and different specialists employ different protocols. The
length of induction treatment is determined by the regimen
chosen and whether or not the patient will undergo ASCT.
Induction treatment is given to candidates for ASCT 3-4
months before the collection of stem cells to lower the
number of tumor cells in the BM as well as peripheral
circulation, alleviate manifestations and prevent EOD.
The frequency of pretransplant cycles differs in Saudi
Arabia (range = 4-8), with some hospitals offering 3 or 4
cycles. If a patient has not achieved complete remission
prior to transplantation, they may receive an additional
two cycles. It was also stressed that the choice to undergo
ASCT is based on the individual’s disease progression
and induction results [21].

Specific preparations for the future ASCT might be
established during this period to help with the treatment
transition. Irrespective of whether an early or delayed
transplant approach is employed, stem cells are collected
during this time. Those who wait until their first relapse
to start ASCT complete 8-12 cycles of initial treatment
and then maintenance therapy until they relapse. For
individuals who do not qualify for ASCT, therapy
includes 8-12 cycles of triplet therapy; then, maintenance
therapy is considered until they progress or experience
intolerable toxicity. Individuals who are not candidates
for triplet therapy get doublet therapy, which comprises
lenalidomide and low-dose dexamethasone [29,30].
A previous Saudi consensus documented that, in their
facilities, they typically follow the NCCN guidelines for
managing newly diagnosed MM (NDMM) patients. For
transplant-eligible patients, the three-drug regimens are
recommended.

One of the institutions has developed a set of
recommendations based on the drugs now accessible.
Induction therapy that includes bortezomib is suggested
by the NCCN in combination with cyclophosphamide,
doxorubicin, lenalidomide, and dexamethasone
[bortezomib-cyclophosphamide-dexamethasone (VCD),
bortezomib combined with dexamethasone (BDX),
and bortezomib-lenalidomide-dexamethasone (VRd)]
[19]. A recently published article reported that, in Saudi
Arabia, 28.4% and 24.9% of the included patients
received the VAD and VCD regimens, respectively.
bortezomib + dexamethasone, thalidomide combined
with dexamethasone, and bortezomib-thalidomide-
dexamethasone were reported in 33 patients (19.5%),
20 patients (11.8%), and 20 patients (11.8%). Following
the induction treatment, complete response or better,
according to the IMWG response criteria, [14] was
reported in 50% of the included patients. The complete
response rate improved to 78.1% following ASCT [7].
A wide range of therapy regimens utilized in real-world
practice to control MM was documented. This variation
was attributed to variables such as the availability of
innovative agents and changing therapeutic strategies.

**Maintenance therapy**

The maintenance therapy significance in MM patients
not candidates for autologous ASCT is still debatable.
For the majority of patients, maintenance therapy is
recommended; this highlights the priority on the
postponement of progression and the possibility of
survival benefits while placing a lower value on the
hazards of ongoing medication. Risk factors and
comorbidities determine the sort of maintenance required.
All patients on lenalidomide maintenance should be
informed about the possibility of developing secondary
malignancies [31].

High-risk MM patients are offered proteasome inhibitor-
based maintenance until progression after 8-12 cycles of
triplet treatment; standard-risk MM patients are offered
lenalidomide-based therapy until progression after 8-12
cycles of triplet therapy. In comparison, frail individuals
are offered single-agent lenalidomide maintenance till
progression unless there is substantial toxicity after nine
cycles of lenalidomide with dexamethasone therapy
[32,33].

While lenalidomide is frequently prescribed for
maintenance therapy in Saudi Arabia, BDX may be a
recommended option for high-risk individuals. Another
study reported that the maintenance therapy post-ASCT
(interferon, thalidomide, or lenalidomide) was used
in 17.8% of the studied patients (n = 169); this low
percentage was due to not involving the maintenance
therapy following ASCT as standard therapy in their
management plan until recently introduced [7].

On the length of maintenance treatment, several
perspectives were voiced in the Saudi consensus. The
majority favored one to 2 years of maintenance therapy,
but some advocated for treating patients until their
condition progressed [21]. The incurability of MM and
the understanding that recurrence might manifest
promptly with life-threatening consequences are
reasons for maintaining treatment in MM. Prospective
studies have shown that maintenance treatment extends
progression-free survival (PFS), but evidence about
whether there is a significant benefit in overall survival
(OS) is equivocal. Most lenalidomide maintenance
trials were conducted in individuals who had undergone ASCT. The significance of maintenance therapy in individuals who have not undergone ASCT has been assessed in a few studies [34-36].

In Saudi Arabia, Abdabou et al. [7] have documented that the influence of ISS staging on the pre- and post-ASCT response was not significant. Death was reported for one patient because of ovarian cancer during the first 100 days after ASCT. The median PFS after ASCT was 30 months, while the median OS time was 202 months [7]. This is likely owing to the accessibility of innovative drugs for salvage treatment, but they are also likely due to the lower median age of the included patients. Future research in Saudi Arabia is needed to investigate any major changes in biology as well as pharmacogenomics.

Relapsed disease

The vast majority of MM patients who survive the first treatment will have a relapse and need further care. Regular surveillance is often performed for relapsed or refractory MM. Treatment for relapsed patients is advised in the case of a clinical relapse or a rise in paraprotein levels. Clinical relapse is suggested if the patient experience CRAB-related symptoms. A twofold of the monoclonal protein over 2 months, with an elevation in monoclonal protein levels of more than 1 g/dl (serum) or ≥500 mg (24-hour urine), verified by two consecutive measures, can also be recognized as a relapsed disease. Patients who have relapsed or are refractory to standard care may be candidates for ASCT, a repetition of the earlier chemotherapy, or an attempt with a different regimen.

Risk classification of myeloma, past therapies administered, and the durability of response to these treatments are all factors that go into deciding which medication to employ [30]. Bortezomib-based regimens constitute the cornerstone of therapy for relapsed/refractory multiple myeloma (RRMM) patients in the United States. Bortezomib may be used either initially or as a retreatment for patients who have achieved a sustained response before disease progression/recurrence [37].

The opinions on the best treatments for RRMM patients in Saudi Arabia differed significantly. This difference has been attributed to the disparity among Saudi Arabian entities regarding resource-related considerations, such as medication expenses, availability, and efficacy, as well as the preference of the patients, and disease-related prognostic factors.

Significance of response

The extent of response is prognostically relevant in MM. Individuals with a minimal residual disease (MRD)-free condition experience a better PFS as well as OS than those who have residual illness after MRD testing [38]. Prior studies have shown that next-generation flow and sequencing techniques can identify MRD outside of the BM with high sensitivity, and such methods can be coupled with functional imaging to identify MRD [39]. Nevertheless, there is no proof from randomized controlled trials that additional therapy improves outcomes for those with MRD-positive disease. The degree of responsiveness, however, is of prognostic relevance. It is uncommon to do an MRD test in Saudi Arabia.

Future therapeutic strategies

The treatment for MM has revolutionized thanks to immunotherapeutic methods. The advancement of these immunotherapy-based therapies for individuals with MM should focus on improving effectiveness without compromising safety.

Future therapeutic strategies for MM include immunotherapy strategies, such as bispecific T-cell engagers and chimeric antigen receptor T cells, which target B cell maturation antigen and other antigens on the surface of myeloma cells, as well as the investigation of Anti-CD38 antibodies in the front line context. Treatment with novel agents, such as triplet or quadruplet induction protocols, has improved outcomes for patients with NDMM. The use of mAb regimens is becoming more common in the frontline context for eligible or ineligible patients for transplantation. Daratumumab, Velcade, Thalidomide, and dexamethasone regimen are now one of the options to treat NDMM transplant-eligible individuals, while Dara-bortezomib, melphalan, and prednison and daratumumab to lenalidomide-dexamethasone are now considered in transplant-ineligible patients [40,41]. However, in Saudi Arabia, VRd is considered the standard of Care for NDMM management. So, Anti-CD38 plus VRd quadruplet regimens are being investigated in transplant-eligible and transplant-ineligible settings.

The GRIFFIN trial, a phase 2 investigation of daratumumab, found an MRD negativity after induction of 21.2% and 5.8% for the D-VRd and VRd arms, respectively [42], while PERSEUS phase 3 study is currently exploring daratumumab combined with VRd [43]. Combinations of Isatuximab with Velcade, Revlimid, and Dexamethasone are also being studied for NDMM in both transplant-eligible and -ineligible patients. Initial readouts of the GMMG-HD7 phase 3 study represented the outcomes of Isa-VRd in transplant-eligible NDMM, which showed 50.1% and 35.6% of MRD negativity post-induction treatment for Isa-VRd and VRd arms, respectively [44].

Conclusions and Recommendations

Despite Saudi residents having access to free healthcare, various possible hurdles to access and individual healthcare-seeking have been documented [45]. There is a scarcity of published articles in Saudi Arabia on MM investigating the characteristics, treatment patterns, and outcomes, although the features of individuals with MM in Saudi Arabia were documented to differ from the same
population in Western countries [46]. This necessitates a single unified and up-to-date national registry to investigate the trends as well as outcomes of Saudi MM patients.

The average time for MM diagnosis and referral from the initial presentation might be as long as a year due to the absence of availability of serum FLC testing at many Saudi healthcare institutes. Early misdiagnosis and complicated referral procedures are responsible for the delay. Some Saudi institutions have developed local management guidelines in response to medicine availability concerns. The majority of institutions, on the other hand, adhere to NCCN criteria.

Educational and quality-improvement initiatives are suggested to be developed to increase adherence and compliance of MM patients. Moreover, a multidisciplinary approach that involves technical personnel with a flow cytometer and other laboratory testing skills is required.

Long-term follow-up by family physicians may be required to evaluate infection, treatment-related adverse effects, as well as renal and thrombotic consequences. The Saudi Arabian referral system was described as confusing and convoluted, with several barriers, including the significant distance between the individual’s house and the healthcare facility, as well as extended waiting lists. The high cost of medicines, availability, compliance with follow-ups, treatment-related side effects, and wide variability in treatment response were underlined as clinical difficulties in the care of MM. To enhance patient compliance and reduce treatment-related serious adverse events, patient-centered therapy is required.

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