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Overview of Multiple Myeloma, Risk Factors, Treatment Approaches

[1]Zuhair Alhasan Jabour, [2]Mohammed Omar Mohammed Alsayed,
[3]Hassan Mohammad Homadi, [4]Mohammed Abdullah Eidoh,
[5]Mohammad Abdullah Mohammad Alkhallaf, [6]Mariam Mohammed Hassan Ayashi,
[7]Sanhan salman Jaber al-malki, [8]Ahmad Saeed Mohammad Alayed,
[9]Manar Mohammad Dabi, [10]Waleed Hassan Ahmed Al Abdulhadi,
[11]Mohammed Awadh Masoud ALQahtani, [12]Ali Omar Moftah

Abstract: **The main goal of this review paper was to overview the Multiple myeloma (MM) in many clinical aspects, and mainly discussing the risk factors, and more importantly the treatment approaches toward this type of malignant bone marrow cancer. We conducted a comprehensive review through the literature using electronic databases; Medline, PubMed and Embase. Eligible studies were sought in PubMed with language restriction to English articles and with human subjects only; search was over these studies published up to January, 2017. Several myeloma (MM) is defined by the neoplastic spreading of a solitary clone of plasma cells generating a monoclonal immunoglobulin. The initial step in coming close to a possible brand-new patient with MM is to verify the diagnosis given that the premalignant phases of myeloma, specifically monoclonal gammopathy of undetermined importance (MGUS) as well as smoldering numerous myeloma (SMM), do not require treatment and may be easily misdiagnosed as MM The therapy of myeloma relies on whether the patient has smoldering myeloma or symptomatic myeloma. Patients with smoldering myeloma are generally observed, with treatment initiated after disease progression to energetic MM. There is no evidence that early therapy of asymptomatic myeloma extends total survival. Patients with symptomatic, energetic myeloma require treatment. This treatment is patient-specific and relies on numerous factors including age, comorbidities, and performance condition.**

Keywords: **Multiple myeloma (MM), risk factors, disease progression, therapy, symptomatic, treatment.**

1. INTRODUCTION

Multiple myeloma (MM) is a mature B-cell neoplastic proliferative disease as well as is additionally referred to as plasma cell myeloma, myelomatosis, or Kahler disease [(1)]. Bone marrow plasmacytosis as well as production of monoclonal immunoglobulin are crucial functions, while symptomatic disease is connected with anemia, hypercalcemia, kidney deficiency, and also osteolytic bone disease [(2)]. MM is the second most common hematologic malignancy and represents 10% to 20% of all hematologic hatreds. Remarkably, its occurrence is anticipated to rise in Western nations taking into account the aging population, given that nearly 30% of patients are aged 75 years or older [(3)]. The 5-year family member survival has actually been approximated at about 41% [(4)]. The epidemiology of MM is a significantly examined area, with numerous conflicts. Older age, positive family history, male sex, black race, as well as genetic factors have actually been referred to as risk factors for the disease [(5)]. Monoclonal gammopathy of unknown value is a problem that comes before MM6 and also is the most important factor connected with the development of MM. Concerning environmental factors, exposure to benzene, oil items, as well as ionizing radiation, in addition to industrial or agricultural profession have actually been acknowledged, whereas tobacco smoking, excessive weight, and nutritional qualities are possibly less implicated yet have actually been resolved in the literary works [(6,7)].

MM evolves from a pre-malignant condition medically recognized as monoclonal gammopathy of unknown value (MGUS). MGUS is present in 3 - 4% of the general population over the age of 50 years [(8,9)]. Considering that MGUS is

mainly asymptomatic and identified commonly as an incidental laboratory finding, only 10% of patients with newly identified MM have a history of pre-existing MGUS. Nevertheless, studies show that MGUS usually comes before MM, as well as is associated with a risk of development to MM of roughly 1% each year [(10)]. Smoldering several myeloma (SMM) is an intermediate phase in between MGUS as well as MM, and also is associated with a greater risk of progression of around 10% annually [(10)].

The main goal of this review paper was to overview the Multiple myeloma (MM) in many clinical aspects, and mainly discussing the risk factors, and more importantly the treatment approaches toward this type of malignant bone marrow cancer.

2. METHODOLOGY

We conducted a comprehensive review through the literature using electronic databases; Medline, PubMed and Embase. Eligible studies were sought in PubMed with language restriction to English articles and with human subjects only; search was over these studies published up to January, 2017. The following search Mesh headings were used in our search through PubMed: (myeloma OR "plasma cell" OR "plasma cells" OR plasmacell OR plasmacytoma OR myelomatosis OR "Kahler's disease" OR "Kahler disease") AND (meta-analysis OR meta-analyses OR "systematic review"). furthermore, references lists of each selected articles were searched for more relevant studies.

3. RESULTS

- **Diagnostic procedures of Multiple myeloma (MM):**

The requirements for diagnosis of myeloma need clonal bone marrow plasma cells, visibility of serum and/or urinary monoclonal healthy protein except in patients with real nonsecretory MM, and evidence of end-organ damages that can be associateded with the underlying plasma cell proliferative disorder, especially hypercalcemia (lotion calcium > 0.25 mmol/L above the ceiling of regular or > 2.75 mmol/L), kidney deficiency (product creatinine > 1.73 mmol/L), anemia (hemoglobin < 10 g/dL or > 2 g/dL below the reduced limit of normal), or bone sores (lytic sores, severe osteopenia with compression fractures or pathologic cracks; CRAB) [(12,13)]. The International Myeloma Working Group (IMWG) and also Mayo Clinic have actually established nearly the same requirements for the medical diagnosis of the plasma cell proliferative problems [(14)]. (**Table 1**) lists the existing IMWG diagnostic standards for MM with small information (as referenced); it likewise lists the analysis criteria for relevant plasma cell conditions that should be set apart from MM [(14)].

Table 1: Diagnostic criteria of MM:

Disorder	Disease definition
Monoclonal gammopathy of undetermined significance (MGUS)	**All three criteria must be met:**
	Serum monoclonal protein <3 g/100 ml
	Clonal bone marrow plasma cells <10% and
Multiple myeloma	**All three criteria must be met except as noted:**
	Clonal bone marrow plasma cells ≥ 10%
	Presence of serum and/or urinary monoclonal protein (except in patients with true non-secretory multiple myeloma) and
	Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically
	Hypercalcemia: serum calcium ≥ 11.5 mg/100 ml or
	Renal insufficiency: serum creatinine >1.73 mmol/l)
	Anemia: normochromic, normocytic with a hemoglobin value of >2 g/100 ml below the lower limit of normal or a hemoglobin value <10 g/100 ml
	Bone lesions: lytic lesions, severe osteopenia or pathologic fractures

Role of the serum FLC assay and Imagining in diagnosis of MM:

The serum FLC assay has three main uses. It has prognostic value in MM, [15] monoclonal gammopathy of unclear importance (MGUS), [16] smoldering MM (SMM) [17] and also singular plasmacytoma of bone [18]. Second, it can be made use of together with lotion protein electrophoresis as well as immunofixation when screening for the presence or absence of a monoclonal plasma cell condition such as myeloma instead of a 24-h pee protein research study. Nonetheless, if a plasma cell proliferative condition is identified, then a 24-h urine healthy protein electrophoresis and immunofixation are needed, and also the lotion FLC assay could not be utilized instead of urine researches. Lastly, the serum FLC examination is useful in keeping an eye on disease course and also feedback to treatment in patients that do not have measurable disease on lotion and protein electrophoresis (consisting of non-secretory myeloma). Measurable disease is defined as lotion monoclonal (M) healthy protein ≥ 1 g/100 ml or pee M protein ≥ 200 mg per 24 h. In patients without measurable disease, there are couple of alternatives available to keep track of disease and the FLC levels will be useful as described in the area below on reaction requirements [16,18].

The baseline analysis works up needed for the medical diagnosis of MM consists of complete blood count, product calcium, lotion lotion, creatinine and pee protein electrophoresis with immunofixation, serum FLC assay, and also bone marrow exam. Additionally, reduced dose whole body computed tomography (CT), or fluoro-deoxyglucose (FDG) positron discharge tomography/CT (PET/CT), or at minimum, simple radiographs of the entire skeletal system are needed to discover osteolytic bone lesions [19]. The osteolytic bone lesions in MM display no brand-new bone development, as well as nuclear medicine bone scans are for that reason not practical [20]. Magnetic vibration imaging (MRI) of the whole body or spine/pelvis is needed in patients with thought SMM, as well as whenever the medical diagnosis of MM is in uncertainty, to search for focal bone marrow lesions [21]. MRI scans are additionally often required in patients with osteolytic bone disease including the spine to dismiss cable compression, and to establish demand for interventional treatments such as vertebroplasty or kyphoplasty.

- **Risk factors associated with MM:**

Lifestyle Factors:

Overweight as well as excessive weight seemed to stand for risk factors for MM, as they were both associated with increased MM incidence as well as mortality [22]. On the other hand, the inverse association in between exercise and also MM risk did not get to statistical value [23]; likewise, no considerable organization linked ever before or current cigarette smoking [24]. An overall safety organization was kept in mind relative to ever alcohol intake, which was particularly apparent at the assessment of wine consumption and also in the subpopulation of women [25].

Occupational Factors:

Occupation as a fireman likewise emerged as a risk factor for MM, conferring roughly 50% increased risk [26]; similarly, profession as a hairdresser was related to increased risk for MM, by around 40% [27]. Work-related exposure to methylene chloride was additionally associated with enhanced MM risk, as shown by the meta-analysis by Liu et alia [28]. On the other hand, amongst null findings, the meta-analysis by Karami et alia [29] did not discover any kind of substantial organization between occupational trichloroethylene direct exposures as well as MM risk. Regarding direct exposure to benzene, the meta-analysis dealing with cohort research studies aimed to a not significant but mild association [30].

- **Treatment approaches of MM:**

The strategy to therapy of newly diagnosed MM is detailed in (**Figure 1**) [31]. The most essential phases of therapy are first therapy, stem cell hair transplant (if eligible), consolidation/maintenance treatment, and therapy of regression. Transplant eligible patients commonly obtain about 4 cycles of first treatment complied with by stem cell collection as well as autologous stem cell hair transplant (ASCT). Selected patients with typical risk MM that respond well to induction can select postponed ASCT; in this strategy stem cells are gathered after 4 cycles of first treatment and cryopreserved for future use (**Figure 1**). Transplant disqualified patients are typically treated for 12 - 18 months. Complying with first therapy and/or ASCT, consideration needs to be offered to consolidation/maintenance treatment. The selection of maintenance and also period of treatment is frequently driven by the visibility or absence of high risk cytogenetic features [32].

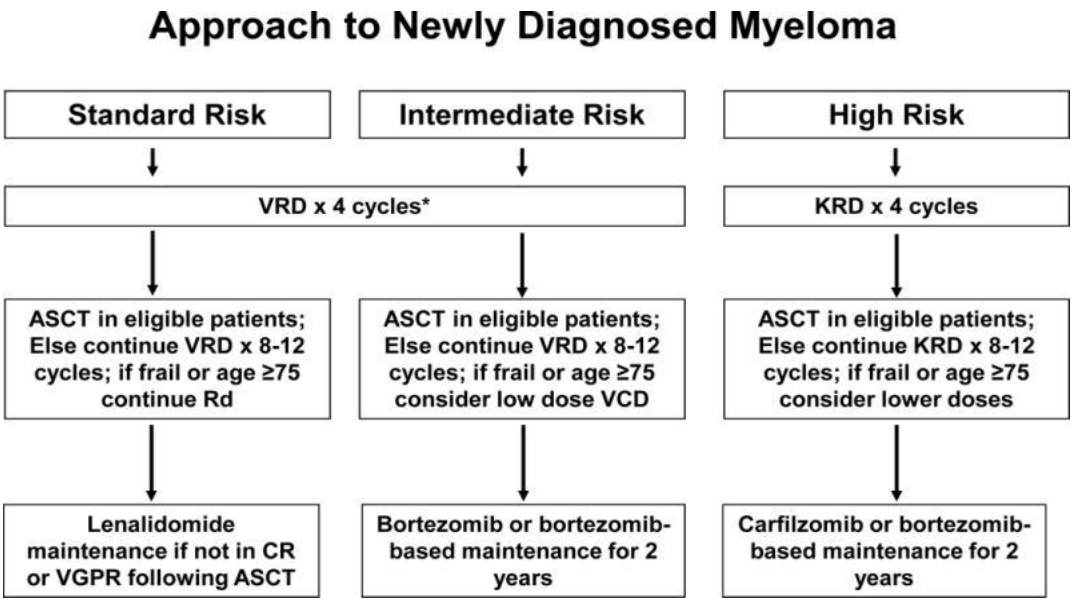

Figure 1: Approach to the treatment of newly diagnosed multiple myeloma

(**Table 2**) summarize the major pharmacological medication used in the treatment of MM [33,34].

Table 2: Selected Drugs with significant single-agent activity in multiple myeloma

Agent	Usual Starting Dose	Postulated Mechanism of Action	Side-effects
Thalidomide	50–200 mg orally days 1–28 every 4 weeks	Binds to cereblon and activates cereblon E3 ligase activity, resulting in the rapid ubiquitination and degradation of two specific B cell transcription factors, Ikaros family zinc finger proteins Ikaros (IKZF 1) and Aiolos (IKZF3); anti-angiogenesis, immunomodulation, and inhibition of tumor necrosis factor alpha. Direct cytotoxicity by inducing free radical mediated DNA damage.	Sedation, fatigue, skin rash, bradycardia, peripheral neuropathy, and constipation. Deep vein thrombosis is a serious adverse event necessitating routine prophylaxis with aspirin or other anticoagulant in all patients. Teratogen.
Bortezomib	1.3mg/m2 subcutaneously days 1, 8, 15, 22 every 28 days	Inhibits the ubiquitin-proteasome catalytic pathway in cells by binding directly with the 20S proteasome complex.	Gastrointestinal, transient cytopenias, fatigue, and peripheral neuropathy.
Lenalidomide	25 mg orally days 1–21 every 28 days	Cereblon mediated ubiquitination and degradation of Ikaros (IKZF 1) and Aiolos (IKZF3); anti-angiogenesis, immunomodulation, and inhibition of tumor necrosis factor alpha. Direct cytotoxicity by inducing free radical mediated DNA damage.	Fatigue, rash, thrombocytopenia, and neutropenia. Deep vein thrombosis is a serious adverse event necessitating routine prophylaxis with aspirin or other anticoagulant in all patients. Diarrhea and leg cramps with long-term use. Teratogen.
Pomalidomide	4 mg orally days 1–21 every 28 days	Same as thalidomide and lenalidomide	Fatigue, rash, thrombocytopenia, and neutropenia. Deep vein thrombosis is a serious adverse event necessitating routine prophylaxis with aspirin or other anticoagulant in all patients. Teratogen.

The triplet regimen of carfilzomib, lenalidomide, dexamethasone (KRd) has actually shown high task in phase II tests, with rigorous full feedback rates (sCR) as well as minimal recurring disease (MRD) negative prices that show up superior to historical outcomes with VRD [35]. These are non-randomized contrasts, and there are problems concerning cardiac poisoning in a tiny proportion of patients with carfilzomib. Additionally, KRD is much more pricey as well as cumbersome compared with VRD. Therefore, we advise the use of KRD at this point only to patients with high risk MM where it might be reasonable to provide a regimen with the highest possible CR rates, as well as based on data from a relapsed MM test that recommends a possible benefit of carfilzomib over bortezomib [36].

Autologous Stem Cell Transplantation:

ASCT boosts complete reaction rates and also extends median general survival in MM by approximately 12 months [37,38]. The treatment-related mortality (TRM) rate is 1- 2%, and the treatment can be performed completely as an outpatient in more than 50% of patients [39]. Eligibility for ASCT is based upon age, efficiency status, and also comorbidities. In the United States the upper age restriction is flexible, and patients can be transplanted as much as age 75 if they are in excellent useful standing with very little comorbidities. On the other hand, in many various other countries, the ceiling for ASCT is 65 years of age. The recommended conditioning routine is melphalan, 200 mg/m2. Research studies are ongoing to establish if the conditioning regimen can be improved with the addition of bortezomib or carfilzomib [40].

Allogeneic Transplantation:

The high TRM and morbidity related to graft versus host disease (GVHD) has actually made traditional allogeneic transplants inappropriate for most patients with MM. Data from randomized tests pertaining to the benefit of allogeneic ASCT are contrasting [41,42]. Despite having a tandem technique of ASCT complied with by a HLA the same sibling donor mini-allogeneic transplant the TRM is high at roughly 10 - 15%. Given exceptional results with present therapy, allogeneic transplantation has a restricted role in MM. We advise it mainly in young patients with high risk MM in second or very first regression who agree to accept a high TRM and also GVHD relevant morbidity in return for a small chance at long-term OS [42].

4. CONCLUSION

Several myeloma (MM) is defined by the neoplastic spreading of a solitary clone of plasma cells generating a monoclonal immunoglobulin. The initial step in coming close to a possible brand-new patient with MM is to verify the diagnosis given that the premalignant phases of myeloma, specifically monoclonal gammopathy of undetermined importance (MGUS) as well as smoldering numerous myeloma (SMM), do not require treatment and may be easily misdiagnosed as MM

The therapy of myeloma relies on whether the patient has smoldering myeloma or symptomatic myeloma. Patients with smoldering myeloma are generally observed, with treatment initiated after disease progression to energetic MM. There is no evidence that early therapy of asymptomatic myeloma extends total survival. Patients with symptomatic, energetic myeloma require treatment. This treatment is patient-specific and relies on numerous factors including age, comorbidities, and performance condition.

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