Fundamentals in the Management of Multiple Myeloma

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SUMMARY

Progress in our understanding of multiple myeloma and its treatment has resulted in a more tailored approach to patient management, with different therapeutics regimens for different patient populations. The decision to initiate therapy depends primarily on the presence of symptoms which has to balance the chance of tumor clearance and against the risks of treatment related mortality. Selection of appropriate initial treatment should be based primarily on patient's characteristics (biologic age, co-morbidities), the disease characteristics (tumor burden and genetic risk profile) and the expected toxicity profile of the different regimens. When treatment begins, in younger transplant eligible patients the goal is to achieve high quality responses with intensive therapies as the quality of response appears to be important surrogates for long-term outcome. In the majority of myeloma patients in whom intensive treatment is not an option due to advanced age and co-morbidities, treatment should emphasize on optimal disease control to obtain symptomatic relief and to maintain a satisfactory quality of life.

The introduction of novel agents has substantially changed the treatment paradigm of this otherwise incurable disease. The utilization of these drugs has moved from relapse setting to the front line setting and has benefited all patient groups. Because of these rapid developments and many treatment options we need good quality clinical studies to guide clinical practice in the management of patients with multiple myeloma.

This review presents an update on current concepts of diagnosis and treatment of patients with multiple myeloma and provides recommendations on tailored therapies with particular reference to the local practice. The information presented herein may be used by the health care providers caring for myeloma patients as a guideline to counsel patients to understand their disease and the treatment better.

KEY WORDS:
Multiple myeloma, Paraprotein, Thalidomide, Bortezomib, Lenalidomide, Treatment

What is Multiple Myeloma and what causes the disease?

Myeloma is a clonal B cell malignancy characterized by aberrant expansion of plasma cells within the bone marrow, as well as cortical bone and other extramedullary sites. The disease was initially described in the 1840s by physicians who observed softening of the bones and infiltrated bone marrow in post-mortem specimens[1]. The unique physical properties of the urinary Bence Jones protein and was initially described in 1847 by a British physician Henry Bence Jones[2], while the discovery of a serum monoclonal protein in patients with plasma cell dyscrasias was made in 1960s by Waldenstrom[3].

Myeloma accounts for 10% of all haematological malignancies[4], and it usually evolves from an asymptomatic premalignant stage of clonal plasma cell proliferation termed "monoclonal gammopathy of undetermined significance" (MGUS). MGUS is present in approximately 3% of the population above 50 years of age and progresses to MM at a rate of 1% per year[5]. Myeloma is responsible for 1.5-2% of all cancer related deaths and 20% of all deaths from haematological malignancies[6]. It is more common in men than women and has a median age of onset of 65 to 70 years.

In most cases, the causes of Myeloma are unknown. However, it has been associated with radiation, benzene, solvent, and pesticide exposure.

What are the clinical manifestations of Multiple Myeloma? (Table I)

Bone diseases in the form of osteopenia, lytic lesions and hypercalcemia are hallmarks of myeloma. Bone pain is the presenting symptom in 70-80% of patients and frequently involves the spine, rib and lower limbs. Bone related complications such as pathological fractures and spinal cord compression are major causes of impaired quality of life and performance status.

Anaemia is common at presentation and important contributing factors include dilutional effect of large amounts of paraprotein in the circulation, suppression of erythropoiesis, renal insufficiency and bleeding. Acute renal failure in the absence of previous renal impairment may follow hypovolemia, and the use of nephtrotoxic agents. Other causes of renal impairment in myeloma include deposition of Bence jones protein, infection, hypercalcemia, hyperuricemia and amyloidosis.

Bleeding is not uncommon manifestation in myeloma. This can occur as a result of abnormal platelet function, interference with clotting factor activities and fibrinolysis, thrombocytopenia and hyperviscosity. Infection is a major cause of morbidity and mortality in myeloma patients. The predisposition to infection is multifactorial in nature. There is usually reduction of normal immunoglobulins (Ig),

This article was accepted: 8 December 2010
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suppression of normal antibody response, neutropenia and impairment neutrophil function.

Neurological complications include compression of the spinal cord and nerve roots, neuropathy associated with tumour infiltration and paraneoplastic syndrome, carpal tunnel syndrome due to amyloidosis, and impaired mental function related to hyperviscosity and hypercalcemia.

How is Multiple Myeloma diagnosed?

Multiple myeloma is a malignant plasma cell disorder in the bone marrow, which produce a monoclonal immunoglobulin (paraprotein or M-protein). This patient-specific M-protein can be detected in the serum or in the urine as free light chains. Identification and quantitation of paraprotein or M-protein on serum and urine protein electrophoresis (SPEP and UPEP) is central in the diagnosis of myeloma. Agarose gel electrophoresis is the usual method of screening for M-protein, while immunofixation electrophoresis performed to characterise the types of heavy chain and light chain. Electrophoresis and immunofixation of a 24-hour urine specimen is necessary because the mass of the M-protein provides an indirect measurement of the patient's tumour mass. The combination of electrophoresis and immunofixation studies improves the sensitivity of detection of M-protein to 97%[6]. Quantitation of M-proteins may be performed by nephelometry but densitometry is preferred. Immunoelectrophoresis shows that the paraprotein is IgG in about 50% of cases, IgA in 25%, IgD in 1% or light chain only M-protein (20%)[7]. Approximately 3% of myeloma is nonsecretory as measured by SPEP and UPEP6 but approximately two thirds of these patients have clonal free immunoglobulin light chains detecBox by the serum free light chain (FLC) assay[8]. Hence, initial assessment of M protein should include serum FLC, as it is required to diagnose nonsecretory or oligosecretory Myeloma and often the first marker of response to treatment or disease progression[9]. Serum FLC is also of value in solitary plasmacytoma, AL amyloidosis, and initial evaluation of MGUS to predict risk of progression to symptomatic MM[10]. Quantitation of serum immunoglobulin levels (IgG, IgM and IgA) is essential as the malignant plasma cells inhibit the development of normal plasma cells resulting in suppression of uninvolved Ig.

The presence of red cell rouleaux formation and leucoerythroblastosis in peripheral blood film is highly suggestive of myeloma. Bone marrow aspiration is mandatory to show and measure marrow involvement by abnormal plasma cells, although the disease may be patchy in nature and sometimes the trephine sample provides better assessment. The bone marrow fragments are usually hypercellular and the cell trails contain numerous abnormal plasma (myeloma) cells. Bone marrow immunohistochemistry and flow cytometry studies are useful to confirm presence of monoclonal plasma cell population.

Investigations to determine the extent of the disease and the presence of end organ involvement include full blood count/peripheral blood film, renal profile, serum calcium and radiological studies. Bone X-ray changes are present in about 80-90% of patients; however the absence of bone lesions does not exclude myeloma. Osteolytc lesions occur most frequently in bones containing red marrow, and are common in the skull. Diffuse osteoporosis is especially common in the spine, leading to wedge-shaped compression fracture. Magnetic resonance imaging (MRI) is more sensitive than conventional skeletal survey in detecting bone lesions and is increasingly used as part of the diagnostic work-up of myeloma. It is recommended to exclude spinal cord compression, soft tissue mass in a localized painful area or for assessing BM involvement in patients with solitary plasmacytoma and smoldering myeloma[11]. The role of positron emission tomography-computed tomography (PET-CT) is less well defined in myeloma but can be useful for detecting extramedullary disease, unsuspected bone lesions, and evaluating patients with plasmacytoma as well as nonsecretory or oligosecretory myeloma[12,13]. PET imaging appears to reliably detect active disease and is consistently negative in smoldering disease and therefore can be used to detect progression to active disease and evaluate treatment response[14,15].

The definition of myeloma and related monoclonal gammopathies requires measurement of the M-protein, bone marrow plasma cells and the presence of end organ damage defined by the acronym "CRAB" (Table II)[7]. This mnemonic refers to organ damage caused by the malignant plasma cell proliferation or by the pathologic M-protein: C = hypercalcaemia; R = renal impairment; A = anaemia; B = bone lesions. Other evidence of organ damage may include symptomatic hyperviscosity, amyloidosis and recurrent bacterial infections (>2 episodes in 12 months). If any of the CRAB criteria are present, then the diagnosis is active (symptomatic) myeloma irrespective of the level of the M-protein or marrow plasmacytosis. If the bone marrow plasma cell percentage is ≥10% or the M-protein is ≥30 g/L and there is no CRAB, then the diagnosis is smoldering (asymptomatic) myeloma. If the bone marrow plasma cell percentage is <10%, the M-protein is <30 g/L and there is no CRAB, then the diagnosis is MGUS[16].

What other investigations are required once a patient is diagnosed with MM?

Since treatment strategy and outcome depend substantially on the burden and prognosis of the disease and fitness of the patient, a thorough work-up designed to determine the disease stage, risk group and vital organ functions is mandatory.

Patients with symptomatic myeloma are categorised according to the disease stage based on the Salmon-Durie staging system[16] or the International Staging System (ISS)[17] (Table III). The original Salmon-Durie staging system[16] was developed by correlating various clinical features of the disease with the estimated total body myeloma cell mass (anaemia, hypercalcaemia, number of lytic lesions, level of M-protein and renal impairment). The newer ISS[17] relates prognosis and survival solely to the levels of beta-2 microglobulin and albumin. The level of beta-2 microglobulin reflects the tumour mass and is now considered a standard measure of the tumour burden. The ISS defines three risk groups: Stage 1 with median survival of 62 months; stage 2 with median survival of 44 months, and

Table I: Clinical Manifestations of Myeloma

	System	Clinical manifestation
1.	Musculoskeletal	Bone pain Pathological fracture Hypercalcemia Tumor/mass (plasmacytoma)
2.	Blood	Anaemia, Thrombocytopenia Prolonged bleeding time Coagulopathy Cryoglobulinemia
3.	Renal	Acute renal failure Chronic renal failure Nephrotic syndrome associated with amyloidosis Hyponatremia Urinary tract infection Hyperuricemia
4.	Immunological	Recurrent infection Hypogammaglobulinemia
5.	Neurological	Compression of the spinal cord and nerve roots Peripheral neuropathy Paraneoplastic syndrome Carpal tunnel syndrome (amyloidosis) Impaired mental function (Hyperviscosity, hypercalcemia)

Table II: Definitions of myeloma and related monoclonal gammopathies.

Standard name	New name	Definition
MGUS (Monoclonal gammopathy of undetermined significance)	MGUS (Monoclonal Gammopathy)	• M-protein<30g/L • Bone marrow plasma cells<10% • No "CRAB"* • No B-cell lymphoproliferative disorder
Smouldering or indolent myeloma	Asymptomatic myeloma	• M-protein ≥30 g/L and/or • Bone marrow plasma cells ≥ 10% • No "CRAB"*
Multiple Myeloma	Symptomatic myeloma	• M-protein in serum or urine • BM (clonal) plasma cells or plasmacytoma • "CRAB"*

*"CRAB" is organ dysfunction characterised by any one of:
C - calcium elevation (>2.75 mmol/L)
R - renal dysfunction (creatinine >173 µmol/L)
A - anaemia (haemoglobin <100 g/L)
B - bone disease (lytic lesions or osteoporosis with compression fractures)

Other: symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (>2 episodes in 12 months)
Adapted from reference no. 7

Table III: Staging system for multiple myeloma

Stage	Durie-Salmon Criteria[1]	ISS Critera[2]
I	All of the following: • Hemoglobin value > 10 g/dL • Serum calcium value normal or < 12 mg/dL • Bone x-ray, normal bone structure) or solitary bone plasmacytoma only • Low M-component production rate ➢ IdG value < 5 g/dL; ➢ IgA value < 3 g/dL ➢ Bence Jones protein, 4 g/24 h	Serum beta-2 microglobulin < 3.5 mg/L Serum albumin ≥ 3.5 g/dL
II	Neither stage I or stage III	Neither stage I or stage III
III	One or more of the following: • Hemoglobin value < 8.5 g/dL • Serum calcium value > 12 mg/dL • Advanced lytic bone lesions • High M-component production rate ➢ IdG IdG value < 7 g/dL; ➢ IgA value < 5 g/dL ➢ Bence Jones protein, 12 g/24 h	Serum beta-2 microglobulin < 5.5 mg/L
Subclassification Criteria **A Normal renal function (serum creatinine level, 2.0 mg/dL)** **B Abnormal renal function (serum creatinine level 2.0 mg/dL)**		

Adapted from reference no: 7, 16, 17.

Table IV: International Myeloma Working Group Uniform Response Criteria for myeloma

Response Category	Response Criteria1
sCR (stringent complete response)	CR as defined below plus: • Normal FLC ratio and • Absence of clonal plasma cells in the BM by immunohistochemistry or immunofluorescence2
CR (complete response)	• Negative immunofixation in the serum and urine, and • Disappearance of any soft tissue plasmacytomas, and • ≤ 5% plasma cells in bone marrow
VgPR (very good partial response)	• Serum or urine M-protein only detected by immunofixation, or • ≥90% reduction in serum M-protein plus urine M-protein level <100 mg/day
PR (partial response)	• reduction of serum M-protein by ≥ 50% + reduction in 24 hour urinary M-protein by ≥ 90% or to < 200 mg/24 h • If the serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required • If serum and urine M-protein, and serum FLC are unmeasurable, a ≥ 50% reduction in BM plasma cells is required provided the baseline BM plasma cell ≥ 30% • In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required
PD (Progressive disease)	Increase of ≥25% from baseline in any of the following: • Urine M- protein (the absolute increase must be ≥200 mg/day) • The difference between involved and uninvolved FLC levels. The absolute increase must be >100 mg/L • BM plasma cell percentage (the absolute % must be ≥10%) Definite increase in the size of existing bone lesions or soft tissue plasmacytomas or development of new lesions
SD (stable disease)	Not meeting criteria for CR, VGPR,PR or PD.

[1]All response categories require two consecutive assessments made at anytime before the institution of any new therapy;
[2]Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is of > 4:1 or < 1:2. FLC = free light chain assay; BM = Bone marrow

Adapted from reference no: 25

Table V: Learning points

1.	A high index of suspicion increase the chance of early diagnosis of myeloma in certain clinical settings, such as spontaneous fracture, renal impairment, proteinuria, normochromic normocytic anaemia and a very high ESR
2.	The absence of abnormal plasma cells in a single bone marrow aspirate does not exclude the diagnosis of myeloma
3.	A significant proportion of patients have serum M-proteins without associated urinary protein
4.	Less than 5% of myeloma patients have no evidence of monoclonal paraprotein (nonsecretory myeloma)
5.	Serum free light chain (FLC) should be done in patients with no detectable M-protein
6.	Magnetic resonance imaging (MRI) is more sensitive than conventional skeletal survey in detecting bone lesions and is increasingly used as part of the diagnostic work-up of MM.
7.	Patient with MGUS and smoldering (asymptomatic) myeloma should have be regularly monitored for the development of active myeloma
8.	Clinicians should avoid treating patients with asymptomatic and biochemically stable patients with specific anti-myeloma therapy
9.	The choice of initial (induction) therapy depends on patient's eligibility for autologous stem cell transplantation (ASCT)
10.	Melphalan/prednisolone/thalidomide (MPT) is the currently recommended induction therapy in elderly patients
11.	In newly diagnosed young myeloma patients, ASCT is considered the standard of care
12.	Bortezomib and lenalidomide have significant activity in both newly diagnosed and relapse/refractory myeloma patients
13.	Biphosphonate therapy is recommended in patients with bone lesions

stage 3 with median survival of 29 months[17]. While these staging systems are simple to apply and widely used, they lack of important prognostic biomarkers of tumour biology such as cytogenetics.

Recently prognostication based on genetic risk classification is gaining importance. Bone marrow aspirates should be obtained for fluorescent in situ hybridization (FISH) analysis for t(4;14), t(14;16) and deletion of 17p, as these abnormalities identify high-risk disease[18]. The use of standard metaphase cytogenetics is often of low yield, but when positive for hypodiploidy, deletion of chromosome 13 or complex karyotype classifies a patient as high-risk disease[19]. The median survival of high-risk myeloma is less than 2 to 3 years even with autologous stem cell transplantation[20]. These high risk patients may benefit from novel therapeutic strategies including bortezomib-containing regimens or allogeneic stem cell transplantation.

Assessment of baseline vital organ functions should be performed prior to commencement of anti-myeloma therapies including a chest radiograph to diagnose occult infection. Assessment of cardiac function by electrocardiograph and echocardiogram is mandatory because most patients are old and chemotherapy regimen may damage the heart. Screening test for human immunodeficiency virus and hepatitis B and C viruses is necessary as chemotherapy may cause reactivation of these infections.

How are patients monitored?

Once diagnosed, patients with smoldering myeloma require frequent monitoring to allow initiation of treatment before the occurrence of organ damage[21]. Upon commencement of myeloma therapies, accurate disease monitoring is critical to enable prompt detection of ineffective therapy and to detect early relapse. Full blood count, SPEP, UPEP or/ and serum FLC, serum calcium, renal function test should be carried out every 3 - 6 months. A repeat bone marrow examination is required not only to confirm complete remission (CR) but also to detect minimal residual disease. Flow cytometry of bone marrow sample can distinguish malignant plasma cells from their normal counterparts on the basis of aberrant expression of several markers (CD19, Cd38, CD56, CD45)[22]. Approximately 40% of patients in CR by standard criteria can be shown to have residual malignant plasma cells by flow cytometry[23] and this residual disease correlates with long-term outcome[24]. Radiological studies may be required in patients presenting with bone or mass lesions.

Standard response assessment is categorized based on quantitation of M-protein and morphological examination of the bone marrow (Table IV). The improved efficacy of myeloma therapies has also brought about a new category of response called stringent complete response (sCR)[25]. In this category, patients who are in CR are examined further by the FLC assay and bone marrow plasma cell clonality study. Clinical trials are underway to determine whether achievement of sCR translates into better clinical outcomes.

When to initiate treatment?

Not all patients with myeloma require immediate treatment upon diagnosis. There is no evidence that early treatment of patients with asymptomatic smoldering myeloma prolongs survival compared withy therapy at the time of symptoms. The decision to initiate therapy depends primarily on the presence of symptoms. Patients with asymptomatic smoldering myeloma including Durie-Salmon Stage 1 have an indolent course for many years without active therapy. These patients should initially be observed at 3 to 6 months interval and treated upon the occurrence of symptoms or if the disease progresses[21]. Disease progression is defined as a sustained 25% or greater risk in M-protein in serum or urine, greater that 25% of increase in plasma cells in bone marrow, development of new lytic lesions, hypercalcemia or increase tumour volume in plasmacytomas[26].

Apart from the presence of symptoms, decision to treat should also depend on patient's medical status and preference. The patient should be involved in the decision process from the start, which has to balance the chance of cure against the risks of treatment related mortality. When cure is the aim, it is desirable to treat patients with the least toxic therapy that will achieve a durable complete remission. These include limiting the number of chemotherapy cycles and restricting radiotherapy to those most likely to benefit from it.

What are the treatment options and outcome in patients with newly diagnosed active myeloma?

The first step in evaluating patients with advanced myeloma is to determine if the patients would be considered a candidate for high-dose therapy and stem cell transplantation (SCT). Eligibility is determined by age, performance status and coexisting co-morbidities.

A reasonable goal of myeloma treatment in younger "transplant eligible" patients (≤ 65 years) is to achieve durable CR, and long-term disease control. To achieve this goal, induction therapy with combination chemotherapies (usually selected from thalidomide, bortezomib, cyclophosphamide, and corticosteroids) which when employed together elicit frequent, rapid, and deep responses. Patients who obtained a good response (CR and VgPR) should receive consolidation with autologous stem cell transplantation (ASCT) followed by maintenance therapy in those failing to achieve a CR or at high risk for early relapse based on prognostic, genetically defined risk factors[21].

In patients with co-morbidities who are ineligible for ASCT, or unwilling to pursue multidrug combination chemotherapies and high-dose chemotherapy, a reasonable goal of treatment is to seek the best continuous disease control with less emphasis on depth of response and more emphasis on obtaining symptom relief and maintaining a satisfactory quality of life. In this situation, a treatment regimen consisting of the fewest drug combination with the least side- effects and adding new drugs in patients not responding to initial therapy may be a logical approach.

Biologically based treatments including the immunomodulatory agents (thalidomide, lenalidomide) and proteosome inhibitor (bortezomib) specifically target myeloma cell interaction within the bone marrow microenvironment; thereby inhibit the growth and survival of myeloma cells. Treatment with these novel agents have shown to be effective in overcoming drug resistance and prolonging response duration in patients with MM[27,28]. Prior to the introduction of novel agents, vincristine, doxorubicin, dexamethasone (VAD) was commonly used as pretransplant induction therapy[29]. VAD has drawbacks, such as requiring continuous intravenous infusion and neurotoxicity with vincristine, which can limit the future use of thalidomide and bortezomib.

The present choices for induction therapy in transplant candidates associated with high remission rates include thalidomide-based, bortezomib-based or lenalidomide-based regimens[30-35]. Melphalan-based therapy should be avoided in patients with newly diagnosed myeloma who are eligible for ASCT, because it can interfere with adequate stem cell mobilization. Patients who are non transplant candidates are treated with melphalan-based induction. Two randomised studies[36,37] have reported that oral combination of melphalan and prednisolone plus thalidomide (MPT) induced a higher response rate, progression free survival and overall survival than the standard melphalan and prednisolone (MP) in elderly, newly diagnosed patients. Hence, the recommended treatment for patients not eligible for high dose chemotherapy and SCT is MPT. Recent data have shown that the addition of bortezomid[38] or lenalidomide[39] to MP was associated with high response rates in newly diagnosed patients aged above 65 years.

In many countries including Malaysia, the access to bortezomib or lenalidomide is restricted, thus the choice of initial therapy will be dictated by the availability of these novel agents. Under such circumstances, referral to a center with access to novel agents through clinical trial is highly recommended. Outside of a clinical trial setting, a thalidomide–based regimen (usually in combination with steroids, cyclophosphamide or anthracyclines) is currently the primary induction therapy of choice for most patients in our practice. The advantages of thalidomide are the ease of administration (oral form), relative lack of myelosuppression and the lack of necessity for dose modification in patients with renal and liver impairment. Bortezomib-based regimen may be preferred in patients with renal failure and who have high risk disease. Recent studies have shown that bortezomib seems to overcome the adverse effects of poor cytogenetics[40,41]. The main drawback of bortezomib is the need for intravenous therapy.

What is the role of stem cell transplantation (SCT)?

SCT can be classifies as a single autologous stem cell transplantation (ASCT), a tandem SCT, or an allogeneic SCT. Tandem transplantation refers to a planned second SCT within 6 months after the first SCT. Allogeneic SCT can be either performed after myeloablative or nonmyeloablative (i.e. "mini" transplant) conditioning regimen.

In general, all candidates for high dose chemotherapy must have sufficient vital organ function. Upper age limits for SCT vary widely from center to center, but in general the overall health of the patient rather than a specific chronologic age is probably most relevant. Hence, advanced age alone is not an absolute contraindication to SCT.

ASCT has been shown to be of value in achieving a higher frequency and depth of CR in patients contributing to prolonged survival and thus[42,43] remains the standard of care following induction therapy for eligible patients. Tandem transplantation would benefit patients who failed to achieve at least a VgPR after the first ASCT[44]. However, because CR rates are now achieved more than 50% to 70% of the time with effective induction therapies combined with single ASCT[45-47] and because responses may be further enhanced by post-transplantation consolidation/maintenance therapies, there is less need to perform tandem transplantation.

Allogeneic SCT transplant has been investigated as an alternative to ASCT to avoid reinfusion of autologous tumour cells and to take advantage of the graft versus tumour effect. However, the lack of suitable donor and the high risk of morbidity and early mortality have limited this approach, particularly for the typical older myeloma population[48]. As it offers the possibility of cure, allogeneic SCT can be considered in very young patients, particularly those who experience early relapses after ASCT or with very high risk features at diagnosis. In order to reduce the treatment related mortality following full myeloablative allogeneic SCT, various "mini-transplant" regimens have been developed for older patients and patients with co-morbidities[49,50].

For patients failing to achieve CR after SCT or with high-risk genetic features, routine maintenance therapy with thalidomide should be considered as it has been shown to increase response rates and prolongs survival[51,52]. However, long term use of thalidomide is associated with significant peripheral neuropathy and hence, lenalidomide seems to the ideal candidate for an effective maintenance therapy[53].

What important adverse effects novel agents?

The safe administration of the novel agents and avoidance of unnecessary dose reduction and discontinuation are important in assuring the best efficacy of treatment. Adverse events associated with these novel agents are largely predicBox, reversible and manageable through close monitoring, dose adjustment or prophylactic interventions.

Thalidomide has been widely used as induction, consolidation and maintenance therapy. It is a synthetic glutamic acid derivative, is poorly soluble in water, and thus no parenteral preparation is available. Neuropathy (peripheral and autonomic neuropathy) and thromboembolism are the major concern with thalidomide. Other side effects include somnolence, constipation, hypothyroidism, skin rash, hepatitis, hypotension and bradycardia[54-57]. Thalidomide is teratogeneic and is absolutely contraindicated in pregnant women.

Bortezomib is the first proteosome inhibitor that has received approval for treatment of newly diagnosed and relapse/refractory myeloma. The most common adverse effects of bortezomib are asthenia, gastrointestinal symptoms, transient thrombocytopenia and peripheral neuropathy (PN). The PN is usually reversible, and preexisting neuropathy and previous neurotoxic agents increases the risk of bortezomib-neuropathy. Bortezomib may enhance the incidence of infections, in particular herpes zoster reactivation[58].

Lenalidomide is an oral immunomodulatory analogue of thalidomide and is currently approved for patients who have received at least one prior therapy. Despite their structural similarity, lenalidomide appears to have a different tolerability profile to that of thalidomide including lower rates of neuropathy, sedation and constipation[59]. Thrombocytopenia and neutropenia were reported as the most common reasons for dose reduction in clinical studies[59-61]. An increased risk of venous thromboembolism and infection has been associated with lenalidomide especially when combined with dexamethasone[61,62].

The cornerstone of managing the side-effects associated with these agents is dose adjustment, interruption of treatment and symptom management. If severe neutropenia develops, cessation of the offending agent, growth factor support and infection prophylaxis are required. Prophylaxis against encapsulated organism, *pneumocystis carinii* pneumonia (PCP), herpes viruses and fungus is recommended in patients receiving high dose dexamethasone, elderly patients and those with a history or recurrent infection. Herpes viruses prophylaxis should be considered in patients receiving bortezomib[63]. Antithrombotic prophylaxis is recommended in high risk patients receiving thalidomide or lenalidomide in combination with dexamethasone[64,65].

What are adjunctive and supportive therapies in MM?

Important advances have been made in adjunctive treatment of myeloma patients. Biphosphonates are essential component of myeloma therapy for minimizing skeletal morbidity and is currently recommended for all myeloma patients who have bone disease including osteopenia66. Patients who are chronic users of biphosphonates should have their renal function monitored and monitored for development of osteonecrosis of the jaw[67].

Low dose radiation therapy is used for palliative treatment of uncontrolled pain, impending pathologic fracture or impending spinal cord compression. Vetebroplasty or kyphoplasty should be considered for symptomatic vertebral compression fractures[68].

Erythropoietin therapy should be considered for anaemic patients, especially those with renal dysfunction. Hypercalcemia should be treated with hydration and frusemide, biphosphonate, steroids and/or calcitonin. The use of nephrotoxic drugs (such as NSAIDS) and intravenous contrast media should be avoided in patients with renal impairment.

Additional important supportive measures include adequate hydration, low impact exercise, adequate pain control and infection prophylaxis. Vaccination against pneumococci, meningococci and *Haemophilus influenza* type b should be considered[69].

What are the treatment options in patients with relapsed NHL?

At the present time, there is no generally accepted standard treatment for relapsed patients. Choice of therapy depends on various factors including age, performance status, prior therapies, response to prior therapies, bone marrow reserve, presence of polyneuropathy, risk for thromboembolism, and renal function[70]. If the relapse occurs at more than 6 months after completion of the induction therapy, patients may be retreated with the same induction regimen. The use of novel agents in the relapse and refractory disease has been associated with as high as 80% response rate[71]. No clear superiority of one novel agent over the other has been demonstrated in randomized clinical trials. Bortezomib is preferred in patients with renal failure as it rapidly reduces tumour load in patients with renal insufficiency. Lenalidomide may be indicated in case of pre-existing peripheral neuropathy, or when a history of thromboembolism may contraindicate its use[62]. It is recommended to use these novel agents in combination with dexamethasone to improve efficacy. Other salvage therapies, include combination chemotherapy (cisplatinum, etoposide, cyclophosphamide, dexamethasone thalidomide)[69].

CONCLUSION

In patients with newly diagnosed multiple myeloma, active treatment should be reserved until symptoms and/or end-organ dysfunction are present or imminent. The aim of current management strategies is to achieve and maintain high quality remission for as long as possible, thus prolonging life and to offer symptom control. The choice of treatment should be tailored according to patient's characteristics (biologic age, co-morbidities), the disease's characteristics (tumor burden and genetic risk profile) and the expected toxicity profile of the different regimens. The introduction of novel drugs regimens such as immunomodulatory drugs and proteosome inhibitors into the conventional treatment regimen has significantly improved the clinical outcome in this otherwise incurable disease. The efficacy of these new regimens should be balanced against their toxicity especially when combined with conventional therapies. Further studies are warranted to define the ideal combination and sequence of these new treatment regimens for each patient perhaps through genetic profiling to help make more directed therapeutic choices.

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MCQ: Fundamentals in the Management of Multiple Myeloma

1. Clinical manifestation of multiple myeloma include:
   a. paraplegia
   b. venous thrombosis
   c. lymphadenopathy
   d. pneumonia
   e. osteosclerotic bone lesion

2. The following are true regarding the diagnosis of myeloma:
   a. The diagnosis can be made in a patient with an elevated serum paraprotein (M-protein) without the need of bone marrow study
   b. The absence of M-protein in the serum and urine excludes the diagnosis of myeloma
   c. If any of the CRAB criteria are present, the diagnosis of multiple myeloma can be made irrespective of the level of the M-protein or marrow plasmacytosis
   d. MRI is more sensitive than conventional skeletal survey in detecting bone lesions
   e. Serum free light chain (FLC) is helpful in the detecting amyloidosis related to myeloma

3. The following features indicate poor prognosis in myeloma:
   a. A high serum beta-2 microglobulin
   b. Hypogammaglobulinemia
   c. Bence Jones proteinuria
   d. Elevated erythrocyte sedimentation rate (ESR)
   e. Deletion of 17p

4. The following are true regarding current treatment strategies in patients with multiple myeloma:
   a. Initiation of specific anti-myeloma therapy is indicated in all patients once the diagnosis has been made.
   b. Melphalan-based regimen is the treatment of choice for transplant eligible patients.
   c. Thalidomide–based regimen is the recommended induction therapy in newly diagnosed myeloma patients
   d. Bortezomib therapy is beneficial for patients with high genetic risk profile
   e. Allogeneic peripheral blood stem cell transplantation is the standard of care for young patients

5. The following drugs and their adverse-effects are correctly paired:
   a. Thalidomide – hypothyroidism
   b. Melphalan – cardiomyopathy
   c. Lenalidomide – deep vein thrombosis
   d. Bortezomib – sensory-motor peripheral neuropathy
   e. Biphosphonate – neutropenia