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Review Article

Multiple myeloma: the disease and its treatment

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ABSTRACT

Multiple myeloma represents a malignant proliferation of plasma cells derived from a single clone. The tumor, its products and the host response to it result in a number of organ dysfunctions and symptoms of bone pain, fracture, anemia, hypercalcemia, susceptibility to infection, neurologic symptoms, clotting abnormalities and manifestations of hyperviscosity. The cause of myeloma remains unexplained but it is associated with few occupations, inflammatory conditions, autoimmune illnesses, viral infections and genetic heterogeneity. Direct interaction between multiple myeloma cells and bone marrow cells activates pleiotropic signalling pathways that mediate growth, survival, migration of multiple myeloma cells and also resistance to chemotherapy. Although myeloma remains incurable, but the use of novel drugs like thalidomide, lenalidomide and bortezomib have resulted in a paradigm change in the therapy of myeloma. Their inclusion in current multiple myeloma treatment regimens have extended median overall survival especially in younger patient population. Recent advances in the molecular genetics have provided opportunities to design highly specific inhibitors of signal transduction pathways that may enhance the efficacy of standard chemotherapy drugs by reducing or altering the pathways associated with cell survival. Despite therapeutic advances, multiple myeloma ultimately relapses and remains an incurable disease. Current research goals are to further increase our knowledge, to identify additional targeted therapies, and to reduce adverse effects and improve response rate. This review focuses on recent clinical advancement in ant myeloma strategies with additional discussion dedicated to emerging drugs that may prove beneficial to patients with this disease.

Keywords: Myeloma, Thalidomide, Lenalidomide, Bortezomib, Therapy

INTRODUCTION

Multiple Myeloma (MM) though lowest in developing countries including Asia, is highest in African-American and Pacific islanders; intermediate in Europeans and North American Caucasians. The higher incidence in more developed countries may result from the combination of a longer life expectancy, more frequent medical surveillance and due to heightened awareness of the disease.[1] Myeloma accounts for 13% of all the hematologic malignancies and 2% of all the malignant diseases. The incidence of myeloma is around 1-9 per 100,000 per year worldwide with higher incidence in North America 7.1 per 100,000 per year.[2,3] Myeloma increases in incidence with age. The median age at diagnosis is 62-65years in industrialized nations and is about a decade less in developing countries (median age in India is 55-56years).[2-4] About 14,400 cases of MM are diagnosed each year, and 11,200 deaths were recorded in the United States in 2001[5] and in 2007, 19,900 cases were diagnosed while 10,790 deaths were recorded in United States.[1] Median survival is 50-55months.[6] The male to female ratio is higher 1.2-1.5:1[4,7] Despite these differences in prevalence, the characteristics, response to therapy and prognosis of myeloma are similar worldwide.[1]

The term multiple myeloma (from Gk. *Myelo-*, bone marrow), was coined in 1873 by Von Rustizky.[8] It is also known as plasma cell myeloma, or as Kahler's disease (after Otto Kahler).[9] Myeloma is an accumulation of malfunctioning or cancerous plasma cells. Despite the name *myeloma*, this form of cancer does not involve myeloid cells, as plasma cells are lymphoid, but is so named because it mainly involves the *myelum* (bone marrow). Most plasma cells reside in the bone marrow,

and myeloma, usually occurs within the marrow of large bones of the body, such as the skull, vertebrae (spine), and hips. Plasma cells that have undergone malignant transformation do so in clumps and usually at many sites, which explains the terminology "multiple myeloma." The net effect is the appearance of large numbers of abnormal cells capable of forming bodily masses, or tumors, with the capacity to advance locally and invade adjacent tissues and organs or spread either through the lymphatics or the blood vessels into distant organs.[10]

ETIOPATHOGENESIS

The cause of MM remains unexplained. Myeloma occurred with increased frequency in those exposed to the radiation of nuclear warheads in World War II after 20-year latency.[1] It has been seen more commonly among farmers,[11] wood workers, leather workers, those exposed to petroleum products and radiation related occupations.[12] Several studies have suggested that myeloma risk is associated with past history of infections,[13] inflammatory conditions, connective tissue disorders, autoimmune illnesses and allergy related disorder. In addition MM and viral infection like HIV[14,] Hepatitis C[15] and Herpesvirus 8[16] may also be associated. There is considerable genetic heterogeneity among patients of MM that impacts disease progression and response to therapy. A variety of chromosomal aberrations like del(13q14) t(11;14)(q13;q32), t(4;14)(p16;q32), MYC rearrangements, hyperdiploidy, and del(17p13) has been noted.[17]

A causal relationship between monoclonal gammopathy of undetermined significance (MGUS) or MM and chronic antigenic stimulation has been suggested.[18] A 2-3 fold higher risk of developing MGUS or MM has been reported in family members of patients with MGUS or MM.[19,20] MGUS is considered to be initial event in the pathogenesis of myeloma. MGUS is a premalignant condition that may progress to smoldering multiple myeloma (SMM), and ultimately symptomatic intramedullary or extra medullary myeloma or plasma cell leukemia. The risk of progression of MGUS to multiple myeloma- related disorder is thus approximately 1% per year.[21]

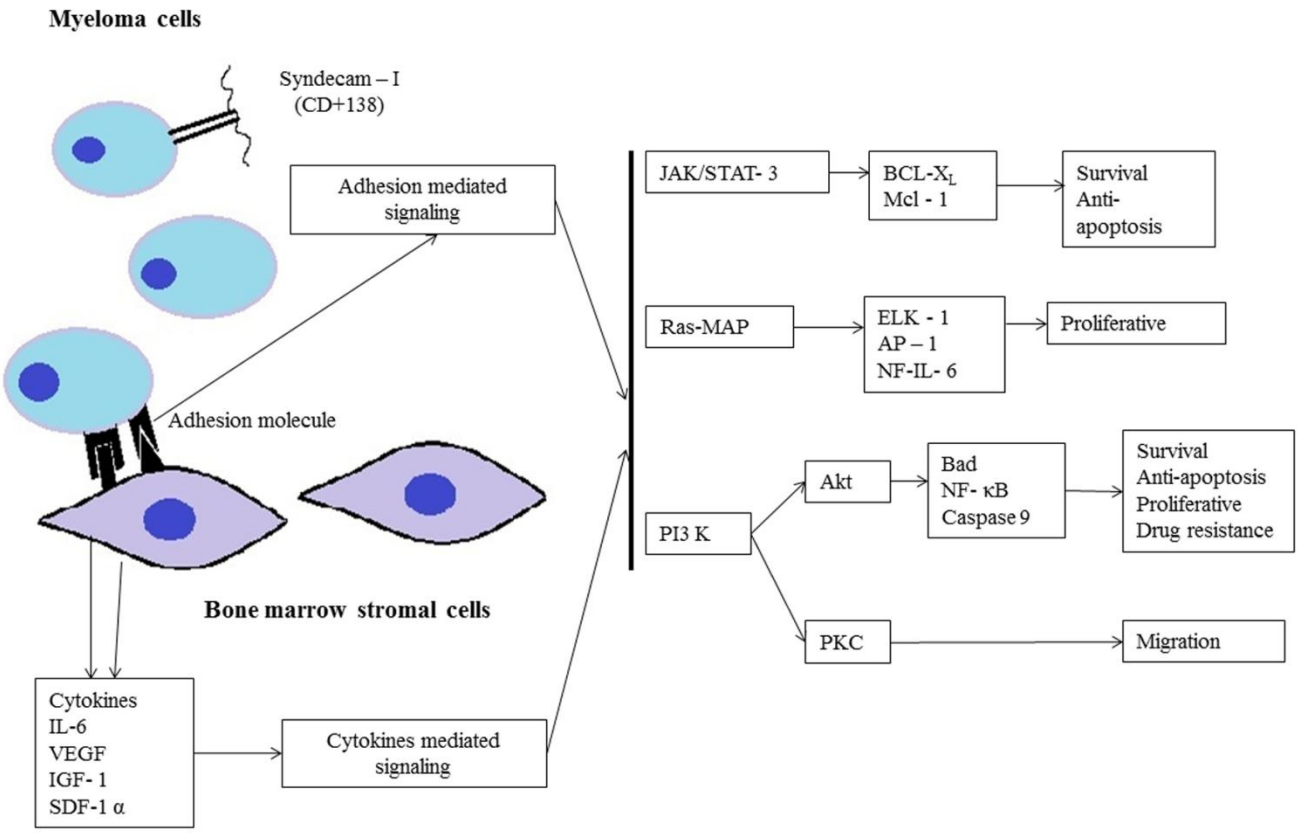
The neoplastic event in myeloma may involve cells earlier in B-cell differentiation than the plasma cell. When B-lymphocytes are made by bone marrow, they are stimulated by antigen in the lymph node into two kinds of plasma cells, the pregerminal center plasma cell (Pre GCPC) and the postgerminal center plasma cell (post GCPC). Pre GCPC is usually short lived. In contrast post GCPC are long lived and they migrate to bone marrow. Multiple myeloma is tumor of post GCPC. In myeloma, tumor cells are mainly localized in bone marrow microenvironment.[22]

Bone marrow endothelial cells (BMECs) and stromal cells (BMSCs) secrete a variety of chemokines such as stromal-derived factor 1 (SDF-1) and insulin-like growth factor 1 (IGF-1) that serve as chemoattractants for MM cells. Multiple myeloma cell binds to bone marrow cell, which stimulates the production of various cytokines like interleukin (IL)-6, Interferon gamma (IFN-γ), vascular endothelial growth factor (VEGF), tumor necrosis factors (TNFs), transforming growth factor-β (TGF-β), and receptor activator of nuclear factor-κB ligand (RANKL).[1] Direct binding of MM cell to bone marrow cells and induced cytokines in turn regulates various signaling pathway like Ras/mitogen activated protein kinase (MAPK), Janus kinase (JAK)/Signal transducers and activators of transcription 3(STAT-3) pathway, Phosphatidylinositol-3 kinase (P13K)/AKT pathway and protein kinase-C (PKC) (Figure-1). IL-6 is among the most important proliferation and survival factors in myeloma.[23] It transmits messages intracellularly through the signal transducing protein gp130, which can activate two pathways: the JAK-STAT pathway[24] and the Ras-MAP kinase pathway.[25] Through the former pathway, the ant apoptotic proteins Mcl-1[24] and Bcl-X_L[26] are upregulated; through the latter pathway, transcription factors, such as Elk-1, AP-1and NF-IL-6[24] are upregulated. Another pathway that is triggered by IL-6 via a protein called PK C-δ are PI3K/Akt and MAPK. The overall effects of all these pathways are prevention of apoptosis, enhancement of multiple myeloma proliferation, drug resistance, and migration of MM cell in the bone marrow milieu. Targeting these signaling proteins may therefore be useful therapeutic strategies.[27]

Other cytokines like IL-1β, up regulates production of IL-6, changes expression of cell adhesion molecules and has been shown to have osteoclast activating factor (OAF) activity. MM cells also secrete VEGF which may account for bone marrow angiogenesis, it also triggers increased growth and motility of MM cells in the bone marrow.[28] Another potential angiogenic molecule in MM is fibroblast growth factor (FGF) which interact with FGF receptors (FGFRs) and it can directly trigger the neovascularization process by stimulating the migration and proliferation of human endothelial cells. Higher basic FGF levels have been found in more advanced stages of multiple myeloma.[29] It is a potent angiogenic factor. IGF-1 directly stimulates the growth of myeloma cell, enhances the myeloma cell responsiveness to IL-6 through MAPK[30] and also inhibiting the apoptosis by increasing the expression of Bad.[31]

CLINICAL MANIFESTATIONS

Multiple myeloma can cause wide range of nonspecific symptoms due to its damaging effect on the bone, the production of the abnormal paraproteins, and by interruption of normal production of blood cells. These signs and symptoms vary according to organ affected and these have been presented below:



IL-6 = Interleukin-6, VEGF = Vascular endothelial growth factor, IGF-1 = Insulin like growth factor, SDF-1$^{\alpha}$ = Stromal derived factor -1$^{\alpha}$, JAK/STAT-3 = Janus kinase/Signal transducer and activators of transcription-3, PI3K = Phosphatidylinositol -3 kinase, PKC = Protein kinase C, BCL-X$_L$ = B cell lymphoma gene, Mcl-1= Myeloid cell leukemia -1,ELK-1 = E twenty six (ETS) like transcription factor, AP-1 = Activator promotor 1, NF = Nuclear factor, Bad = Bcl2 associated death promotor.

Figure 1: Pathogenesis of multiple myeloma.

Bone pain

Bone pain is the most common symptom in myeloma, affecting nearly 70% of the patients and it usually involves the back and ribs. Persistent localized pain in a patient with myeloma usually signifies a pathologic fracture. Myeloma bone disease is due to the overexpression of RANKL by bone marrow stroma. RANKL activates osteoclasts, which resorb bone. The resultant bone lesions are lytic in nature which are best seen in plain radiographs, which may show "punched-out" resorptive lesions (including the "pepper pot" appearance of the skull on radiography).[1]

Hypercalcemia

Hypercalcemia occurs in 18 - 30% of patients. The symptoms of hypercalcemia include nausea, vomiting, tiredness, mental confusion, fatigue, constipation, abdominal pain, and weight loss. Raised calcium levels may impair kidney function.[27]

Renal failure

Renal failure occurs in nearly 25% of myeloma patients, and hypercalcemia is the most common cause of renal failure. Glomerular deposits of amyloid, hyperuricemia, recurrent infections and frequent use of nonsteroidal anti-inflammatory agents (NSAIDs) for pain control, use of iodinated contrast dye for imaging, bisphosphonate use, and occasional infiltration of the kidney by myeloma cells all may contribute to renal dysfunction. It may also be due to tubular damage from excretion of light chains, also called Bence Jones proteins, which can manifest as the Fanconi syndrome (type II renal tubular acidosis).[1]

Infection

Many patients with myeloma develop infections with Gram-positive (e.g. *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Haemophilus influenzae*) and Gram-negative (*Pseudomonas aeruginosa*) microorganisms. The greatest risk period for the occurrence of infection is in the initial few months after

the start of chemotherapy.[10,32,33].The most common infections are pneumonias and pyelonephritis. The increased risk of infection is due to immune deficiency resulting from diffuse hypogammaglobulinemia, abnormalities in complement functions, and therapeutic agents like dexamethasone.[1]

Hyperviscosity

Hyperviscosity refers to an increase in the viscosity or resistance to flow of the blood and is due to excessive production of proteins by the malignant plasma cells, specifically monoclonal (M) proteins that attach themselves to platelets and interfere with platelet function. Signs and symptoms of hyperviscosity are bleeding, bruising, headache, fatigue, sleepiness, neurologic symptoms, confusion, visual disturbances and retinopathy.[1]

Anemia

Anemia is the most common clinical feature of MM and it is usually normocytic, normochromic and related to the replacement of normal marrow by expanding tumor cells, inhibition of hematopoiesis by factors made by the tumor and also mild hemolysis. Patients may have megaloblastic anemia.[27] Granulocytopenia and thrombocytopenia are very rare. Clotting abnormalities may be seen due to the failure of antibody-coated platelets to function properly or because of interaction of the M component with clotting factors I, II, V, VII, or VIII.[1]

Neurological symptoms

Neurologic symptoms occur in 5-15% of patients, and there are many causes for it like hypercalcemia (causes produce lethargy, weakness, depression, and confusion), hyperviscosity (leads to headache, fatigue, visual disturbances, and retinopathy), bony damage and collapse, (leads to cord compression, radicular pain, and loss of bowel and bladder control) and infiltration of peripheral nerves by amyloid (can be a cause of carpal tunnel syndrome and other sensorimotor mono- and polyneuropathies). Sensory neuropathy is also a side effect of thalidomide and bortezomib therapy. Spinal cord compression is a medical emergency and requires immediate treatment to relieve the pressure and prevent permanent damage.[1]

DIAGNOSIS

The diagnosis of myeloma is established by the presence of bone marrow plasmacytosis (>10%), serum and/or urine M component and end organ damage. Bone marrow plasma cell are CD138+ and monoclonal. Proliferation of MM is measured by the plasma cell labeling index (PCLI), β_2 microglobulin or gene expression profiling (GEP). GEP has been utilized to identify high risk patients and to differentiate between normal plasma cells, those in MGUS, MM and extramedullary plasmacytomas.[34,35] The M protein can be detected by serum protein electrophoresis in 82% of patients and by immunofixation in 93%.[7] The serum M component will be IgG in 53% of patients, IgA in 25%, and IgD in 1%. Upto 20% of patients will have only light chains either kappa/lambda (κ/λ) in serum and urine.[1] Serum free light chain (FLC) ratio κ/λ is useful in diagnosing and monitoring the course of the disease and response to therapy particularly in patients with light chain myeloma who do not have detectable M protein on serum or urine electrophoresis.[36] FLC κ/λ ratio (reference range 0.26-1.65) is used to distinguish polyclonal elevations seen with renal dysfunction from monoclonal elevation.[37]

The International Myeloma Working Group (IMWG) has established a criteria 'CRAB' based on end organ damage to distinguish asymptomatic myeloma from active disease. These include C hypercalcemia, R renal insufficiency, A anemia and B bone lesion.[38]

The most important differential diagnosis in patients with myeloma involves their separation from individual with MGUS, SMM and primary amyloidosis. Patient with MGUS or SMM should be identified and not treated unless symptoms develop or laboratory abnormalities progress because they remain stable for many years. Patients with MGUS have M protein <3g/dl, absence of lytic bone lesions, anaemia, hypercalcemia and bone marrow with <10% plasma cells. The patients with MGUS go on to develop multiple myeloma. For Patients with serum M protein <1.5g/dl, IgG subtype and normal serum FLC κ/λ ratio the risk of conversion is low (5% at 20years). Patients with serum M protein >1.5g/dl, IgA subtype and abnormal serum FLC ratio have a higher risk for conversion to myeloma (58% at 20years), and they should be followed up at 3-6 month interval. [39] SMM is characterized by the presence of a serum M protein (IgG or IgA≥ 3g/dl), ≥ 10% of atypical plasma cells in the bone marrow and absence of target organ damage. The probability of progression to MM is 10% per year for the first 5years, 3% per year for next 5year and 1% for the next 10years.[40]

PROGNOSIS

Survival of patients with MM depends on disease stage. Although median survival is approximately 3 years,[7] some patients with MM can live longer than 10 years.[41-43] Since 1975, the Durie-Salmon staging system has been used to stratify patients with MM.[44] but it has limitations, especially in the categorization of bone lesions.[45,46] Greipp et al[47] have developed the new International Staging System (ISS), which overcomes the limitations of the Durie-Salmon staging and divides patients into 3 distinct stages solely on the basis of serum β2-microglobulin and albumin levels. The ISS is the most widely used method of assessing prognosis (Table-1). Cytogenetic analysis of myeloma cells may be of prognostic value, the deletion of chromosome 13, translocations of t(4;14), t(14;16) t(14;20) confers poorer prognosis. By contrast a favourable prognosis has been observed in the presence of t(11;14), t(6;14) or

hyperdiploidy.[17,48,49] Syndecan -1 (also known as CD138) is found on the surface of almost all myeloma cells, whether they are in the bone marrow or the blood. The myeloma cell can use it to attach itself to the other cell. Syndecan-1 can be shed into the serum by the action of enzymes called proteases, means it accumulates in the serum of myeloma patients. High level of syndecan -1 in the serum correlates with the poor prognosis.[22]

Table 1: International Staging System (ISS) for Multiple Myeloma.[47]

	Level	Median Survival (Months)
Stage 1	Serum β2-microglobulin < 3.5 µg/mL. Serum albumin ≥3.5 g/dL	62
Stage II	Serum β2-microglobulin= 3.5-5.5 µg/mL. Serum albumin ≤3.5 g/dL	44
Stage III	Serum β2-microglobulin > 3.5 µg/mL.	29

TREATMENT

Patients with symptomatic and/or progressive myeloma require therapeutic intervention. Therapy can significantly prolong survival and improve the quality of life of myeloma patients. Patients with inactive or SMM should be closely monitored without instituting therapy, as no survival benefit/ advantage has been demonstrated by treating asymptomatic multiple myeloma.[50,51]A long term plan for managing the disease should be formulated before instituting therapy for symptomatic disease (Figure 2). In general MM therapy includes symptomatic supportive care & systemic therapy. Symptomatic supportive care to prevent serious morbidity from the complications of the disease which includes adequate hydration, bisphosphonates, management of renal failure, anemia and infection. Systemic therapy is to control the progression of myeloma and is tailored to patients' age, comorbidities and preferences. Patients who are <65 years of age with no major co-morbid conditions are usually eligible for high dose therapy and autologous stem cell transplantation (HDT&ASCT) whereas patient with >65 years of age with cardiac or renal disease are not eligible for HDT & ASCT. Local treatments, such as radiation therapy is often given to patient with MM in order to control or kill the cancer cell in a certain area.

Treatment of myeloma in patients eligible for transplantation

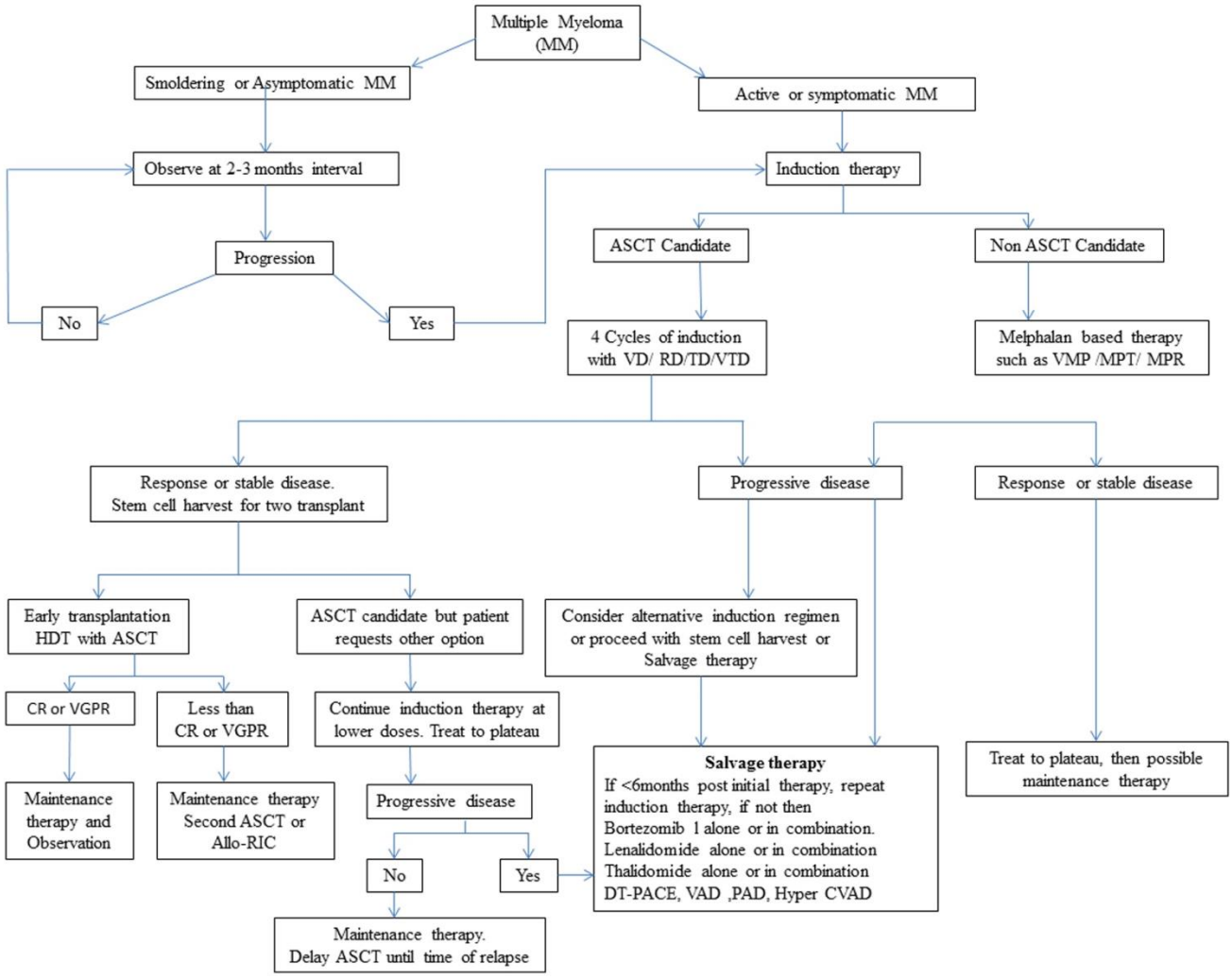
Treatment of the young patient population, aged <65 years or older if in good performance status, should be based on HDT/ASCT. After initial induction therapy, stem cells are collected to perform HDT/ASCT. Subsequent consolidation and maintenance strategies are recommended.

Induction therapy

The aim of induction therapy is maximal disease control to collect tumour-free peripheral blood stem cells (PBSCs). Typically patients are treated with approximately four cycles of induction therapy before stem cell harvest. This includes patients who are transplantation candidates but who wish to reserve ASCT as a delayed option for relapsed/refractory disease. Such patients can resume induction therapy following stem cell collection until a plateau phase is reached; reserving ASCT for relapse.The sensitivity to the initial induction therapy is measured by the M-protein which is the most important predictor of complete response (CR). Earlier vincristine, doxorubicin, dexamethasone (VAD) was used as pre-transplant induction therapy. However, VAD has drawbacks such as requiring an intravenous indwelling catheter and neurotoxicity from vincristine. The other induction regimen used was cyclophosphamide, idarubicin and dexamethasone. With the use of these conventional chemotherapy regimens the post-transplant CR rate has been about 35% and the median overall survival (OS) of six years in the best circumstances.[52] Induction therapy with melphalan-based regimen should be avoided as it can interfere with adequate stem cell mobilization.[53] The current availability of new drugs such as thalidomide, lenalidomide and bortezomib have provided the framework for improving the results of ASCT.

At present, a combination of immunomodulators (thalidomide or lenalidomide and dexamethasone) or proteasome inhibitors (bortezomib and dexamethasone) are used for induction. The overall response rate (ORR) with these combinations are superior to four day continuous infusion of vincristine, adriamycin and oral dexamethasone (VAD).[54] Thalidomide emerged as the first important new drug treatment for myeloma following recognition of its anti-angiogenic effects in the 1990s. Thalidomide is given orally and has immunomodulatory anti-inflammatory and apoptotic effects. Thalidomide/dexamethasone (Thal/Dex) was approved by the US Food and Drug Administration (FDA) in 2006[55] for use as pre-transplant induction regimen. The use of Thal/Dex in newly diagnosed myeloma was initially based on three phase II clinical trials.[56,57] A case-control study of 200 patients demonstrated that response rates with VAD were significantly lower compared to Thal/Dex combination (76% v/s 52%).[58] Preliminary results from other randomized trials confirm these findings.[59,60] The Eastern Cooperative Oncology Group (ECOG) in 2006 compared Thal/Dex to dexamethasone alone in 207 patients.[61] The best response within four cycles of therapy was significantly higher with Thal/Dex as compared to dexamethasone alone (63% versus 41%). Dexamethasone alone has also been used as induction therapy, with an objective response rates of approximately 45%,[61] which is significantly lower as compared to newer induction regimen and the early mortality rate (first 4 months of therapy) associated with dexamethasone is over 10%,

reflecting the toxicity and ineffectiveness of this regimen. Consequently, single-agent dexamethasone is no longer recommended as initial therapy.[62] Thalidomide combined with dexamethasone is an effective pre-transplantation induction regimen.[63] The most frequent adverse effects seen with thalidomide based regimens were somnolence, constipation, neuropathy and fatigue. The less common ones were edema, venous thrombosis, skin rash, bradycardia, neutropenia and hypothyroidism. Thalidomide is a teratogenic drug and is contraindicated in pregnancy. In elderly patients the use of thalidomide may cause disturbing constipation and neuropathy.[64]



ASCT = Autologous stem cell transplantation, Allo-RIC = Dose reduce intensity conditioning allogenic transplantation, MP = Melphalan Prednisolone. V= Velcade/Bortezomib, R = Revelimid/Lenalidomide. T = Thalidomide, D = Dexamethasone, DT- PACE = Dexamethasone, Thalidomide, Cisplatin, Doxorubicin, cyclophosphomide, Etopside. VAD = Vincritine, Doxorubicin, Dexamethasone. PAD = Bortezomib, Doxorubicin, Dexamethasone. Hyper CVAD = Cyclophosphomide, Doxorubicin, Vincristine, Dexamethasone. HDT = High dose chemotherapy, CR = Complete response, VGPR = Very good partial response

Figure 2: Approach to the treatment of multiple myeloma.

Lenalidomide (Revlimid) is an oral thalidomide analogue and acts by similar mechanisms, targeting both signalling pathways within the malignant plasma cell and the bone marrow microenvironment. Lenalidomide is frequently effective even in patients whose myeloma is resistant to thalidomide. A phase II trial conducted at the Mayo Clinic demonstrated remarkably higher activity (91% response rate) with the Len/Dex regimen in newly diagnosed myeloma.[65] ECOG tested Rev/Dex (40mg/day for 4days per week) versus Rev/low-dose Dex (40 mg dexamethasone once weekly)[66] which showed that toxicity rates are significantly higher with Rev/high-dose Dex compared to Rev/low-dose Dex. The early mortality rate (first 4 months) in the Rev/low-dose dexamethasone was probably the lowest mortality (0.5%) reported in any large phase III newly diagnosed myeloma trial therefore making it one of the safest pre-transplant induction regimens for myeloma. A combination of lenalidomide

and low dose dexamethasone (40 mg once a week) is the standard schedule,[67] and approved by FDA in June 2006.[68] Lenalidomide is free of somnolence, but causes mild constipation, minimal neuropathy, neutropenia, thrombocytopenia and thromboembolism therefore, requiring close monitoring. Effective contraception is also required because of its teratogenic potential and it require dose modification in patients with renal failure.[64] There has been some concern about collection of progenitor cells after lenalidomide therapy[69] but this appears to be minimized if a combination of cyclophosphamide and a growth factor is used for mobilization.[70] More recently, a new chemokine receptor inhibitor plerixafor has been studied for its effects on stem cell mobilization. Plerixafor in combination with G-CSF has been successfully used in patients failing previous mobilization attempts. It overcomes the negative effects of lenalidomide on stem cell mobilization.[71-74] These results led to the FDA and European Medicines Agency (EMA) approval of plerixafor in combination with G-CSF in 2008 and 2009, respectively, in patients with non-Hodgkin lymphoma and MM.[75] At present, stem cell collection is usually done after 4 cycles of lenalidomide and dexamethasone.[76] Patients receiving thalidomide or lenalidomide in combination with high-dose steroids need routine thromboprophylaxis with coumarin or low-molecular weight heparin (LMWH). Aspirin can be used instead in patients receiving only low doses of dexamethasone (40 mg, 4 days a month or lower) or prednisone in combination with thalidomide, provided no concomitant erythropoietic agents are used.[62]

Another regimen with high anti-myeloma activity is the association of bortezomib (Velcade) and dexamethasone.[77,78] Bortezomib is a potent, reversible, and selective inhibitor of the 26S proteasome targets the myeloma cell and the bone marrow microenvironment and acts by inhibiting the binding of myeloma cells to stromal cells and decrease bone marrow triggered angiogenesis.[79] In newly diagnosed myeloma, bortezomib has shown response rates of approximately 40% as a single-agent,[80] 70-90% in combination with dexamethasone (Vel/Dex),[77,81] or with thalidomide and dexamethasone (VTD). A combination of bortezomib with dexamethasone, doxorubicin, lenalidomide or thalidomide and melphalan has synergistic activity and may overcome resistance to either agent.[82-85] Harousseau and colleagues reported superior response rates and long-term outcome with Vel/Dex compared to VAD.[86]

The main drawback of bortezomib-based therapy is the need for intravenous therapy. No adverse effect on stem cell mobilization has been noted. No increased risk of deep vein thrombosis (DVT) was observed with bortezomib- based regimen (<5%). The most common adverse events seen were sensory neuropathy (31%), constipation (28%), myalgia (28%) and fatigue (25%)[81] and higher frequency of herpes zoster infection.[87] For patients with neuropathy, the dose of bortezomib can be reduced to 1 mg/m^2 or even 0.7 mg/m^2. However, the benefit of bortezomib-based combinations is in elderly patients with impaired renal functions (creatinine clearance <60 ml/minute), and those with high risk cytogenetics including the presence of t(4;14), t(14;16) translocation or a 17p deletion.[80]

Thus, treatment with thalidomide, lenalidomide or bortezomib in combination with dexamethasone is associated with higher response rates than conventional therapy. It is not clear which of these combinations is better. The toxicity profile, cost analysis, quality of life and long term follow up data will help to choose one combination over the other.[88] The real impact of increased CR rates, when incorporating novel agents in the pre-transplant induction regimens, on the long-term post-ASCT outcome require more prolonged follow-up.

High dose chemotherapy (HDT) with Autologous Transplantation (ASCT)

High-dose chemotherapy followed by ASCT is considered the gold standard in the initial therapy of younger patients with MM. The stem cell must be collected using granulocyte-colony stimulating factor (G-CSF), with or without cyclophosphamide before the patient is exposed to conditioning therapy. The backbone of conditioning therapy is melphalan, administered at doses ranging from 100 to 200 mg/m^2, dependent on age and preexisting comorbidities.[89] During the past decade, a number of randomized and nonrandomized studies have shown that treatment with high dose melphalan therapy (HDT) (200 mg/m2) followed by ASCT is associated with CR rates of 40%–50% with improved OS and event-free survival (EFS).[90-92] ASCT prolongs survival in MM, but its timing (early vs delayed) is controversial. Three randomized trials showed that survival is similar whether ASCT is done early (immediately after 4 cycles of induction therapy) or delayed (at the time of relapse as salvage therapy).[93,94] In a randomized trial of the Spanish Programa para el Estudio de la Terapéutica en Hemopatía Maligna (PETHEMA) group, patients responding to induction therapy had similar OS and PFS with either ASCT or 8 additional courses of chemotherapy,[92] suggesting that the greatest benefit from ASCT may be in those with disease refractory to induction therapy.[95,96] Overall, given the inconvenience, adverse effects of prolonged chemotherapy, cost and other issues, early ASCT is still favorable , especially for patients younger than 65 years with adequate renal function.[97] However, with effective new agents to treat MM, some patients and physicians may choose to delay the procedure. The need for early ASCT is an important question for future clinical trials.

A second ASCT is recommended by the NCCN Guidelines within 6 months of the initial ASCT for those patients who did not achieve at least a very good partial remission (VGPR) after the first ASCT.[89] Various studies reported that two successive HDTs (Double or Tandem ASCT) are more effective than single HDT in the subset of patients who do not achieve a CRs or (VGPR) to the

first transplant.[98,99] Kumar et al have recently reported the result of a metaanalysis of six randomized trials where the response rate was significantly better with double transplant, whereas the mortality rate was higher with no improvement in OS for patients treated with tandem transplant.[100] The two major shortcomings of ASCT are that myeloma is not eradicated even with the large doses of chemotherapy and that autologous peripheral stem cells are contaminated by myeloma cells or their precursors (Graft versus myeloma effect GVM), so this procedure is not curative and most patients relapse.

Allogeneic stem cell transplantation remains the only potential curative treatment for MM patients. The advantage of allogeneic transplantation are the lack of graft contamination with tumor cells and the presence of GVM effect.[101,102] However only 5-10% of patients are candidate for conventional allogeneic transplantation due to high transplant related mortality (TRM) from severe graft versus host disease (GVHD), availability of HLA-identical sibling donor in only one third of patients and age of the patients. Because of its high transplant-related mortality (TRM) the myeloablative allogeneic transplantation with conventional conditioning has been almost universally replaced by the so called dose reduced intensity conditioning allergenic transplantation (Allo-RIC/ Miniallogeneic transplantation). During the past decade, a number of studies have explored the role of Allo-RIC from an HLA-identical sibling donor after debulking with ASCT but results are still controversial.[103-107] At this time, miniallogeneic transplantation is investigational. It should be considered only in the context of clinical trials in standard-risk MM.

Treatment of myeloma in patients not eligible for transplantation

In patients not eligible for ASCT the conventional therapy has consisted of intermittent pulses of an alkylating agent, melphalan and prednisone (MP) administered for 4-7 days every 4-6 weeks. With these regimens the ORR has been between 40–50% and the CR rate less than 5% with median survivals of about three years. The addition of novel agents thalidomide, bortezomib and lenalidomide with either MP or dexamethasone have shown improved results. Various trials comparing MPT (melphalan-prednisone-thalidomide) with MP have showed that a combination of MPT is superior to MP in elderly patients in terms of CR, OS and EFS.[108-111] MPT was associated with a higher risk of neurological adverse events (10% vs 1%), infections (10% vs 2%), cardiac toxicity (7% vs 4%) and thromboembolism (12% vs 2%) as compared to MP regimen.[109] Antithrombotic prophylaxis with LMWH, warfarin, or daily aspirin is recommended when using MPT.[112] A study compared the association of Thal/Dexa with MP, Thal/Dexa produced a significantly higher ORR (68% *vs.* 50%) but was more toxic in elderly patients thus resulting in a significantly shorter OS (41.5 *vs.* 49.4 months).[113]

In a phase I/II trial, safety and efficacy of MP in combination with lenalidomide (MPR) in newly diagnosed elderly myeloma patients were studied.[114] At the maximum tolerated dose (lenalidomide 10 mg plus melphalan 0.18 mg/kg), partial response (PR) was 85%. One year EFS and OS were 92% and 100% respectively. EFS of patients with deletion of chromosome 13 or chromosomal translocation (4; 14) were not significantly different from those who did not have shown such abnormalities. By contrast, patients with high-levels of serum β2-microglobulin experienced shorter EFS in comparison with those with low-levels of β2-microglobulin. Adverse events were mainly related to hematological toxicities (neutropenia 66%) whereas non-hematological side effects were less frequent and were febrile neutropenia (8%), cutaneous rash (10%) and thromboembolism (6%). Rate of thrombotic complication was low with daily low dose aspirin prophylaxis.

An ECOG compared lenalidomide/dexamethasone at full doses of dexamethasone versus lenalidomide/dexamethasone at a dose of dexamethasone of 40 mg weekly. The OS at one year was significantly longer with lenalidomide/low-dose dexamethasone due to a significantly lower toxicity. This difference was higher in patients older than 65 years.[67]

The combination of MP with bortezomib (MPV) was superior to MP in overall response rate (71% *vs.* 36%), CR rate (30% *vs.* 4%), EFS (median, 24 *vs.* 16 months) and OS (82% *vs.* 69% at two years).[80] Importantly, MPV was superior to MP in all prognostic subgroups, including high-risk cytogenetics such as t(4;14), t(14;16) and 17p deletion. Sensory neuropathy could be an important limitation of bortezomib in these elderly patients.[79,115] Once the maximum response is achieved (after 6-9 cycles of MPT or MPR or 4-6 cycles of MPV patients can be kept on observation.

It seems that the association of MP or dexamethasone with a novel agent such as thalidomide, bortezomib or lenalidomide will become the standard of care for elderly patients with MM. The first choice will depend on the patient age and clinical status as well as on the disease characteristics.

Maintenance therapy

The concept of maintenance therapy may open new avenues for new treatment approaches in myeloma. Several trials have explored the benefits of maintenance strategies after ASCT or after induction therapy in transplant-ineligible patients in terms of response rate and survival. Maintenance therapy aims to prolong remission in long-term tumor control and to reduce the risk of relapse.[116] Maintenance therapy with interferon alfa-2 is of limited value and is seldom used.[117] A study by Berenson et al suggests that prednisone may be useful for maintenance therapy. With 50 mg vs 10 mg of prednisone taken orally every other day, PFS (14 vs 5 months) and overall survival (37 vs 26 months) were significantly

longer. But the side-effects of long term steroid therapy preclude its routine use. [118] The incorporation of new drugs as maintenance therapy appears to produce better results. The results of 3 randomized studies using thalidomide showed improved EFS.[119-121] The OS was better in two studies[119,120] but neuropathy (7-27%) led to discontinuation of thalidomide in a proportion of patients. Lenalidomide may overcome this problem due to better tolerability.[122] Compared to placebo, lenalidomide maintenance significantly delays the time to progression (TTP). Specifically, McCarthy and colleagues[123] showed an estimated median TTP of 42.3 months for the lenalidomide arm versus a TTP of 21.8 months for the placebo arm at 17.5 months from ASCT. Similarly, Attal and associates[124] observed a median PFS from diagnosis of 52 versus 34 months in lenalidomide versus placebo-maintained patients. Advantages in terms of PFS by lenalidomide maintenance have also been demonstrated by Palumbo and colleagues[125] in the nontransplant setting. Bortezomib also showed promising results as a maintenance therapy, suggesting that bortezomib maintenance may favorably impact time to recurrence.[126] Additional studies are needed to determine the role of routine maintenance in myeloma, especially the use of lenalidomide, which has a better safety profile than thalidomide for long-term maintenance.

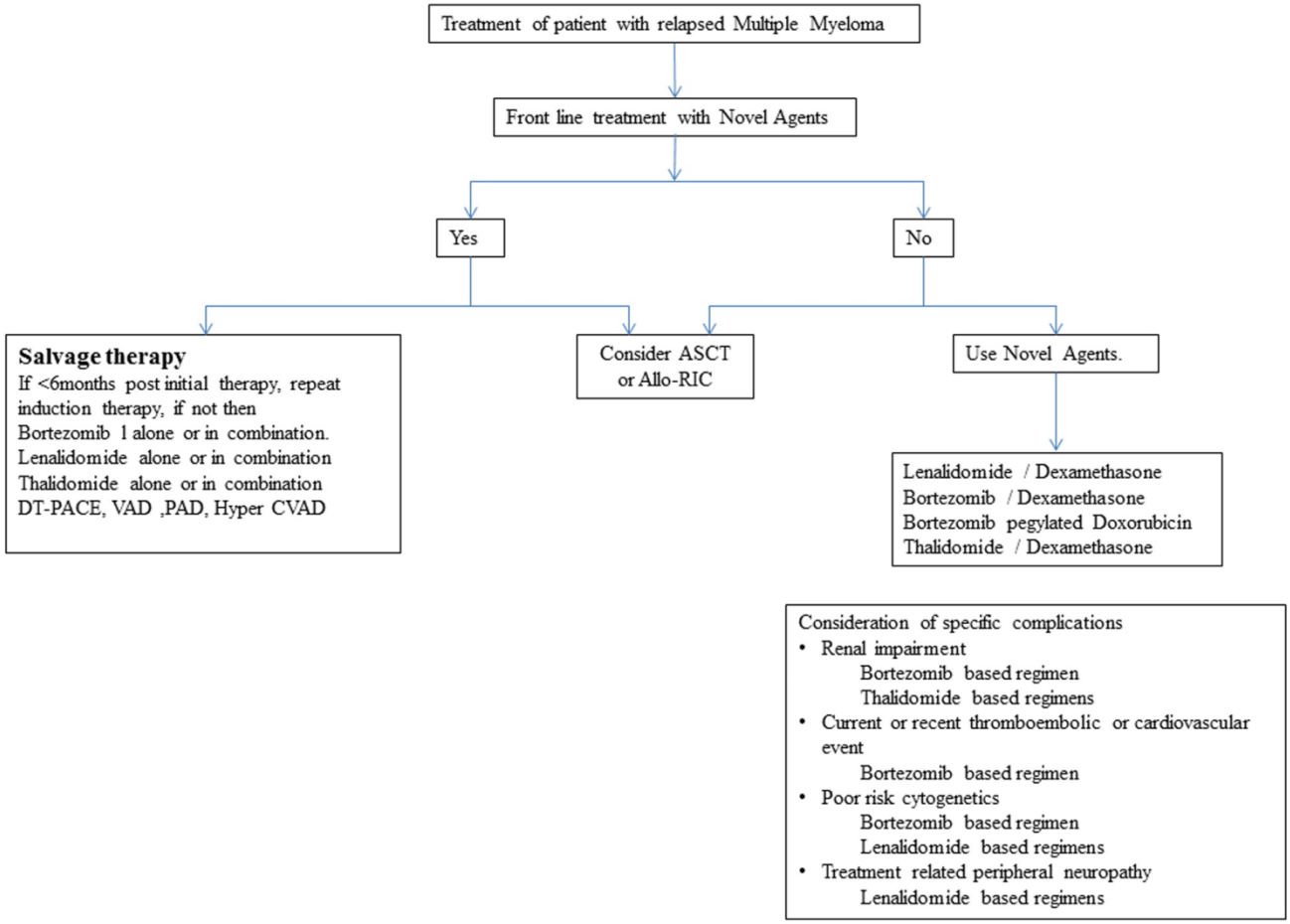


Figure 3: Treatment of relapsed multiple myeloma.

Treatment of patients with relapsed /refractory disease

Multiple myeloma relapses eventually in almost all patients and the treatment of patients with relapsed/refractory disease constitutes a real challenge. Treatment choices depend on previous therapies, duration of response and toxicities, age at the time of relapse, type of relapse (*aggressive*/*indolent*) and presence of high-risk cytogenetic features.[127] Thalidomide-dexamethasone (Thal/dexa), lenalidomide-dexamethasone (Len/dexa) and bortezomib-dexamethasone (Velc/Dexa) based combinations can be used for patients who relapse after MP/VAD chemotherapy (Figure 3).[128,129] If relapse occurs more than 6 months after therapy ended, the initial chemotherapy regimen should be reinstituted. If relapse occurs after a shorter period of time from induction, treatment options include HDT/ASCT (Patients for whom

stem cells were cryopreserved early in the disease) or Allo-RIC (young patients with preferably HLA-matched donors) or switch to a new regimen.[130-133]

Strategies approved in the relapsed setting include bortezomib alone or in combination with pegylated liposomal doxorubicin, and lenalidomide in combination with dexamethasone.[129,134] A combination of bortezomib with pegylated liposomal doxorubicin (PLD) is superior to bortezomib alone in VGPR plus CR (27 *vs.* 19%), TTP (median, 9.3 *vs.* 6.5 months) and OS at 15 months (76% *vs.* 65%).[134] Similarly the combination of lenalidomide plus dexamethasone was superior to dexamethasone alone in ORR (60% *vs.* 22%), CR rate (15% *vs.* 2%), median time to progression (TTP) (median 11 *vs.* 5 months) and OS (median, 29.6 *vs.* 20 months).[135,136] Lenalidomide is active in thalidomide or bortezomib-pretreated patients. Bortezomib alone or in combination with dexamethasone is active in thalidomide / lenalidomide pretreated patients. Bortezomib administered as a single agent induces an ORR and a CR rate up to 43% and 9% respectively.[78,137]

Ongoing studies are evaluating double, triple, and quadruple combinations, as well as additional targeted novel agents. Thalidomide has been combined with a variety of agents, such as dexamethasone, cisplatin, cyclophosphamide, and etoposide (DT-PACE).[138] Safety and efficacy of lenalidomide plus pegylated liposomal doxorubicin or cyclophosphamide and dexamethasone have been additionally evaluated.[139,140] Among the novel agents currently tested in myeloma, are the new immunomodulatory drug pomalidomide and proteasome inhibitorv carfilzomib are the most promising. Notably, activity of pomalidomide was also observed in patients refractory to thalidomide, lenalidomide, or bortezomib.[141,142] In the relapsed/refractory setting, an overall response of 30% was achieved by drug pomalidomide, alone or in combination with dexamethasone. The dose-limiting adverse effect was myelosuppression.[143,144] Carfilzomib in contrast to bortezomib, has an irreversible mechanism of action.[145,146] Although high response rates were demonstrated in patients previously treated with lenalidomide, bortezomib, and HDT/ASCT, even higher response rates were observed in bortezomib-naïve patients.[147] Reported toxicity was mainly hematologic A larger randomized phase III trial is planned to assess the combination of carfilzomib plus lenalidomide plus dexamethasone in the setting of relapsed disease.

SUPPORTIVE THERAPY

Supportive care is as important as the treatment of primary tumor. Supportive therapies in MM aim to prevent and treat bone disease and its complications, thromboembolic events, renal impairment, hyperviscosity, infections, and anemia (Table 2). It is symptomatic and as discussed below:

Table 2: Supportive therapies in Multiple Myeloma.

Bone disease	Bisphosphonates. Kyphoplasty, Vertebroplasty. Radiation.
Anaemia	Erythropoietin
Hypercalcemia	Hydration and Bisphosphonates, eventually calcitonin.
Infections	Immunoglobulin.
Thromboembolic events	Anticoagulation strategies in case of thalidomide or lenalidomide-based regimens.
Renal failure	Hydration. Avoid NSAIDs and nephrotoxic drugs.

Bone Lesion

Patients with symptomatic bone disease or asymptomatic patients whose bone imaging suggests decreased bone density benefit from therapy with bisphosphonates.[148] Indeed, monthly infusions with zoledronate or pamidronate reduce skeletal complications (hypercalcemia, fractures, and pain). Zoledronic acid may be superior to pamidronate.[149,150] Treatment can be continued (once in 6 months) in patients with persistent bone disease or osteoporosis and should be resumed in case of disease progression or relapse. Patients with persistent localized bone pain can get benefit from vertebroplasty and kyphoplasty.[151]

Anaemia

The various causes of anaemia in myeloma are inadequate levels of erythropoietin (present in up to 50%), iron, folate and vitamin B_{12} deficiency.[152] Following response to antimyeloma therapy, anaemia responds in most patients. Randomized placebo-controlled trials have shown that symptomatic anemia often is improved by administration of erythropoietin.[153,154] Erythropoietin (40,000 U subcutaneously, weekly) or darbepoetin (200 µg subcutaneously every 2 weeks) is beneficial. Blood transfusions are indicated for patients with symptomatic anemia who do not benefit from other therapies.

Infections

Prophylaxis against *Pneumocystis carinii* pneumonia should be considered in all patients receiving high-dose corticosteroidal therapy. A small randomized placebo-controlled trial of trimethoprim-sulfamethoxazole in 57 patients with newly diagnosed MM showed benefit with routine prophylaxis administered with the first 2 cycles of chemotherapy.[155] Alternative agents such as ciprofloxacin, levofloxacin, or cephalosporins for *P carinii* pneumonia prophylaxis should be considered. Intravenous gamma globulin given every 3 to 4 weeks is indicated if patients have recurrent serious infections associated with severe hypogammaglobulinemia. Intravenous immunoglobulin may be considered as an

adjuvant in patients with serious infections.[33,107,156] Nephrotoxic antibiotics, like aminoglycosides should be avoided in patients with compromised renal functions.[10,64]

Renal failure

The main causes of renal failure in MM are cast nephropathy (80%), light chain deposition (5%-6%) and amyloidosis (<10%). Other factors like dehydration, hypercalcaemia, hyperuricaemia, infections and nephrotoxic drugs (e.g. aminoglycosides and NSAIDs) are reversible and should be corrected[4] and avoided.[157,158] Maintenance of a high urinary output (3 L/d) is important in preventing renal failure in those with high levels of monoclonal light chains in the urine. Dexamethasone or bortezomib alone, or bortezomib with dexamethasone with/ without doxorubicin, or thalidomide with dexamethasone or VAD are preferred in patients with renal failure. Plasmapheresis should be considered in such patients in an attempt to prevent irreversible renal damage.[159]

Deep Vein Thrombosis (DVT)

Patients undergoing thalidomide- and lenalidomide-based therapies are at high risk for thromboembolic events and benefit from the regular use of anticoagulants. Based on risk-stratification analysis, aspirin, low-molecular-weight heparin, or warfarin may be administered. The duration of prophylaxis is 4-6 months.[64,160]

Hyperviscosity Syndrome

Infrequently, patients with MM develop hyperviscosity syndrome. Plasmapheresis promptly relieves the symptoms and should be performed if the patient has signs or symptoms of hyperviscosity.[161]

NEW THERAPIES / FUTURE PERSPECTIVES/ NEW INVESTIGATIONAL AGENTS

Despite the development of more effective therapies for multiple myeloma (MM) over the past decade, nearly all patients will eventually experience progressive disease or disease relapse and require further therapy. Designing the next generation of therapies for relapsed and refractory disease will depend on understanding the complex molecular pathogenesis of MM and mechanisms of resistance. Direct interaction between MM cells and bone marrow cells activates pleiotropic signaling pathways that mediate growth, survival, and migration of MM cells as well as resistance to chemotherapy. The bone marrow also secretes growth factors and cytokines that maintain MM cells and inhibit apoptosis. Therefore, successful therapeutic strategies must target not only the MM plasma cell but also the bone microenvironment. The benefit of immunomodulatory drugs such as thalidomide and lenalidomide and the proteasome inhibitor bortezomib in relapsed/refractory MM is related to their ability to target both. Novel agents and combination strategies are building on the success of these agents and targeting synergistic pathways. Among that, the most promising are the immunomodulatory drug pomalidomide, which can be active even in patients refractory to lenalidomide, the proteasome inhibitor carfilzomib, active in patients resistant to bortezomib and with an acceptable safety profile, and the histone deacetylase inhibitors (HDAC), particularly vorinostat (SAHA) and panobinostrat (LBH 589).[162,163] Carfilzomib is approved by FDA on July 2012[164] for the treatment of patients with MM who have received at least two prior therapies, including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of the completion of the last therapy. Pomalidomide has shown promise in phase II trials and a new drug application for it has been submitted to the FDA.[165]

Histone deacetylase inhibitors, particularly vorinostat and panobinostrat act by increasing the productions of proteins that slow cell division and cause cell death. They have shown limited efficacy when used alone.[162,163] A promising approach is the addition of a these agent as a third drug to a well-established regimen to obtain an additive or a synergistic effect in the so-called triple rescue regimens. A study reported, addition of panobinostrat, to either bortezomib/dexamethasone (PBD) or lenalidomide /dexamethasone (PLD) resulted in a synergistic effect in all: MM cell lines, fresh myeloma cells and plasmacytoma murine models.[166] Another study also showed that PBD may be effective in relapsed and velcade refractory patients.[167] The combination of panobinostat, Velcade, and dexamethasone is currently being tested in a Phase 3 clinical trial, Panobinostat is also being studied in combination with other common anti-myeloma drugs, including Revlimid, carfilzomib and pomalidomide.[167] Vorinostat, another HDAC inhibitor being studied for the treatment of myeloma, was recently shown to have a small impact on PFS when used in combination with Velcade in relapsed/refractory myeloma patients.[167]

Bone marrow endothelial cells secrete CXCL12, also known as stromal derived factor 1-alpha (SDF-1α), which is a ligand of CXCR4 and plays a pivotal role in myeloma bone marrow homing. Thus, the CXCL12/CXCR4 stimulates motility of myeloma cell, increases the expansion and migration of plasma cells *in vivo*, also stimulates bone marrow angiogenesis resulting in myeloma progression. In fact, serum levels of CXCL12 correlate nicely with bone marrow angiogenesis,[168] so administration of a CXCL12 antagonist will decrease angiogenesis. Martin et *al*[168] reported that prolonged exposure to hypoxia and hypoxia-inducible transcription factor (HIF) strongly up-regulated CXCL12 expression in myeloma plasma cells. It has been suggested that targeting HIF might be an interesting strategy in the attempt to inhibit angiogenesis and disease progression in MM.

Multiple myeloma represents the malignancy with the richest cancer/ testis antigen CTAs. CTAs are a promising class of tumor antigens and are regulated by

epigenetic mechanisms such as promoter methylation and histone acetylation.[169] Several CTAs have been detected in many MM cell lines and primary tumor samples from patients with MM and MAGE-C1/C17 was the most frequently expressed CTA in MM.[170] Various studies describe the role of MAGE-C1/C17 in the proliferation, disease progression, cell adhesion, chemosensitivity and apoptosis.[171,172] So CTAs might constitute important targets for novel anti-myeloma specific therapies. Other molecules, monoclonal antibodies, particularly anti-IL-6 antibodies,[173] AE491[174] shark cartilage compound, Arsenic trioxide[175] and antibiotic Biaxin[174] is being evaluated in clinical trials at multiple centers for treatment of MM and are under various phases of clinical trial and once the results are confirmed, then these are likely to be incorporated in the first line treatment of myeloma.

CONCLUSION

From all the above it becomes evident that considerable progress has been made in the management of MM over the past 2 decades. From being incurable, the disease is now a chronic illness. The availability of newer drugs thalidomide, lenalidomide and bortezomib has provided an opportunity to achieve higher response rates. Initial induction therapy with these newer drugs followed by consolidation with intensive chemotherapy and ASCT in younger patients without major co-morbid condition, and combination of newer drugs with melphalan and prednisolone or dexamethasone in the elderly patients are the preferred treatment in MM patients. We can see an improved long-term outcome for patients with MM through several other actions /interventions like (i) the possible use of a tailored front-line therapy in an individual patient like for patients with renal failure - bortezomib, thalidomide and/or doxorubicin combination could be an option, for patients with pre-existing peripheral neuropathy - lenalidomide and dexamethasone is preferred, for patients at high risk of DVT bortezomib-based regimens can be used safely[94], (ii) selecting the best rescue regimens after relapse and exploiting all the effective drugs preferably in a sequential use according to previous drug exposure, depth and duration of response and previous toxicity, (iii) a careful evaluation of response, serological relapse and clinical progression ensuring a timely, appropriate administration of therapy, (iv) adequate prophylaxis and/or management of toxicities, in particular peripheral neuropathy and deep vein thrombosis and (v) supportive care. We are certain that the application of all the above will show real enhanced survival perspectives for both young and elderly patients with multiple myeloma. For the next decade we can anticipate the consolidation of the novel treatment approaches as well as the incorporation of a new generation of drugs with more specific molecular targets in myeloma treatment programs.

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