Review Article

Recent advances in the management of multiple myeloma

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ABSTRACT

Multiple myeloma is a disease of malignant plasma cells in the bone marrow. Interaction of malignant plasma cells with the bone marrow microenvironment plays a key role in the pathogenesis of the disease. The introduction of two new classes of molecules, namely immunomodulators (e.g. thalidomide, lenalidomide), and proteasome inhibitors (e.g. bortezomib) has led to improvement in the management of myeloma. Induction therapy with these novel drugs in combination with dexamethasone is associated with higher response rates including complete response in one-fourth of patients with bortezomib combinations. Further consolidation with intensive chemotherapy supported by autologous stem cell transplant in young, eligible patients results in complete response in 50%–70% of patients with improved survival. Simplified criteria for staging, uniform response criteria, more sensitive methods for detection of residual disease (immunofixation and free light chain assay), and recognition of potential adverse cytogenetic and genomic abnormalities have further refined the management of patients with myeloma. Along with earlier diagnosis, improved treatment and better management of complications have resulted in longer disease control and survival with a better quality of life.

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INTRODUCTION

Multiple myeloma (MM) is a neoplastic disease of the plasma cells. These accumulate in the bone marrow and produce a monoclonal protein (immunoglobulin), usually IgG or IgA, often referred to as M or myeloma protein. Myeloma accounts for 13% of all haematological malignancies and 2% of all malignant diseases. The incidence of myeloma is 1–9 per 100 000 worldwide with a higher incidence in North America (7.1 per 100 000 population for men and 4.6 per 100 000 for women) and lower in Asia (China, Japan and India).[1,2] The aetiology of myeloma is unknown; a causal relationship between monoclonal gammopathy of undetermined significance (MGUS) or MM and chronic antigenic stimulation has been suggested.[3] A 2- to 3-fold higher risk of developing MUGS or MM has been reported in family members of patients with MUGS or MM.[4,5]

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CLINICAL PRESENTATION

In industrialized nations, the median age at diagnosis is 62–65 years; it is about a decade less in developing countries (median age in India is 55–56 years).[1,2,6] According to the Surveillance Epidemiology and End Results (SEER) Cancer Statistics review (USA, 2001) about 35% of myeloma patients were younger than 65 years, 28% were in the age group of 65–74 years and 37% were older than 75 years.[1] In a study from India, 12% of patients were younger than 40 years,[6] compared with 2% in a study from Mayo Clinic (USA).[7] The peak incidence of myeloma is between 65 and 75 years of age and the male-to-female ratio is higher, 1.2 to 1.5:1.[6,7] Most patients present with bone pains (70%–80%) (backache being most common), anaemia (60%–70%) and renal failure (one-third). Less commonly, soft tissue masses, neurological symptoms (<10%) and recurrent bacterial infections (10%) may be the presenting symptoms. Other clinical manifestations include disorders of metabolism (hypercalcaemia or hyperuricaemia) or amyloidosis, cryoglobulinaemia and the hyperviscosity syndrome.[6,7]

DIAGNOSIS

Bone marrow examination, serum and urine electrophoresis for the presence of paraprotein (myeloma or M protein) and immunofixation, and skeletal survey are essential components of the initial work-up for myeloma. A skeletal survey including X-rays of the skull, pelvis, ribs, vertebrae, shoulder girdle and long bones is required. Radiologically, typical myeloma lesions are multiple, osteolytic and have sharp punched-out margins. These lesions are well seen on X-rays of the skull, ribs and pelvic bones. In the vertebrae, there may be partial or complete compression and the pedicles are often spared. Vertebral destruction may be associated with a paraspinal soft tissue mass. Spinal cord compression may occur secondary to extradural involvement or vertebral collapse. Pathological fractures of the humerus or neck of femur may be seen. Extramedullary myeloma generally occurs in the upper respiratory tract, usually in the paranasal sinuses or pharynx.[8] Osteoporosis is a frequent finding in myeloma; it is multifactorial in aetiology and includes diffuse marrow involvement. It may occur with or without bone lesions. Osteoporosis alone cannot be considered a sign of bone disease that requires treatment unless it causes bony deformity such as vertebral collapse.[9]

Magnetic resonance imaging (MRI) is useful in patients with spinal cord compression, solitary plasmacytoma, in symptomatic

patients with a negative bone survey, and to delineate areas requiring radiation therapy or surgical intervention.[9] Recent studies suggest that MRI can detect involvement of the vertebral marrow in 50% of patients with indolent myeloma (defined as asymptomatic myeloma with <4 osteolytic lesions and normal renal function). One-third of patients considered to have a solitary plasmacytoma have bone marrow abnormalities consistent with MM.[9] Data on the role of whole body positron emission tomography (PET) in myeloma are limited.[10,11] A PET-CT scan is superior, identifying both extramedullary and medullary lesions in patients with negative X-rays.[10] A recent study reported whole-body MRI to be better than PET in the assessment of disease activity with a higher sensitivity and specificity.[11] The routine use of bone scan is not helpful.[8] Serum free light chain (FLC) ratio (κ/λ ratio) is useful in monitoring the course of the disease and response to therapy particularly in patients with light chain myeloma who do not have measurable disease on serum and urine electrophoresis.[12]

The diagnosis of myeloma is established by the presence of paraprotein (either in the serum or urine or both), bone marrow plasmacytosis, and bone lesions on skeletal survey or localized plasma cell infiltration. On electrophoresis, paraprotein (M protein) is either IgG (60%–70%), or IgA type (15%–20%) and 15% of patients have only light chains (either κ or λ). The International Myeloma Working Group has established criteria (based on end-organ damage, acronym CRAB) to distinguish asymptomatic myeloma from active disease. These include C hypercalcaemia (serum calcium 0.5 g/dl above the upper limit of normal or >10.5 mg/dl), R renal insufficiency (serum creatinine >2 mg/dl), A anaemia (haemoglobin 2 g/dl below lower limit of normal) and B bone lesions (lytic lesions or osteoporosis with compression fracture). Other features may include recurrent bacterial infections (>2 episodes in 12 months), amyloidosis and symptomatic hyperviscosity.[13]

MGUS is a premalignant condition that may progress to myeloma. It is defined by the presence of M protein <3 g/dl, absence of lytic bone lesions, anaemia, hypercalcaemia or renal insufficiency and a bone marrow with <10% plasma cells. Patients with MGUS are asymptomatic, have no evidence of end-organ damage but do have a 1% annual risk of progression to myeloma. The risk of conversion to myeloma may depend upon the amount of M protein and immunoglobulin isotype and the ratio of serum FLC. For patients with serum M protein <1.5 g/dl, IgG subtype and normal serum FLC ratio (0.26–1.65), the risk of conversion to myeloma is low (5% at 20 years). Such patients can be followed up once a year. Patients with serum M protein >1.5 g/dl, IgA subtype and abnormal FLC ratio have a higher risk for conversion to myeloma (58% at 20 years) and should be followed up at 3–6-month intervals.[14]

About 15% of patients have a smoldering or asymptomatic myeloma, characterized by the presence of a serum monoclonal protein (IgG or IgA ≥3 g/dl), ≥10% of atypical plasma cells in the bone marrow or both, in the absence of target organ damage. The probability of progression to symptomatic or active myeloma is 10% per year for the first 5 years, approximately 3% per year for the next 5 years and 1% for the next 10 years.[15] The current approach is to keep such patients under close observation and to start therapy only in the presence of target organ damage. Selected patients with osteopenia may be considered for bisphosphonate therapy.[12]

PROGNOSTIC FACTORS

Stage

The Durie and Salmon staging system, described in 1975, was based upon the levels of haemoglobin, serum calcium, serum creatinine, serum and urine paraprotein (M protein), and the number and size of bone lesions.[16] This provided a simple and practical estimate of tumour burden. Patients were categorized as stage I, II or III, depending on the degree of anaemia, hypercalcaemia, and levels of M protein in the serum and urine or bone lesions. In addition, patients without or with serum creatinine of ≥2 mg/dl were categorized A or B. One of the major limitations of this staging system was that the number of lytic bone lesions on plain X-ray were observer-dependent. This staging has now been replaced by the International Staging System (ISS) which has been validated in several clinical studies. ISS (Table I) uses a combination of serum β2 microglobulin and serum albumin, and correlates well with long term outcome.[17] However, ISS cannot distinguish MGUS or smoldering myeloma from active or symptomatic myeloma. Also, stage III ISS is a composite group, where serum β2 microglobulin can be elevated because of myeloma burden as well as renal failure (may be present in 20%–30% of patients at diagnosis).[18]

Cytogenetics

A number of cytogenetic abnormalities have been identified in myeloma. Hyperdiploidy (characterized by multiple trisomies of chromosomes 3,5,7,9,11,15,19 and 21) is identified in 50%–60% of patients with myeloma and is associated with longer survival. Structural abnormalities such as del 13 are detected in about 50% of patients, del (16q) in 20%, del (17p) in 10%, and gain of 1q21 in 30%–43% of patients. Translocation involving immunoglobulin heavy chain gene locus t(4;14) (p16.3;q32) occurs in 14%–20% of patients and t(14;16) (q32;q23) in 2%–10% of patients. These are associated with a poor prognosis.[19–21] Hyperdiploidy and cyclin D translocations (t[11;14] and t[6;14] are associated with a good prognosis. Secondary genetic events such as deletion p53, and del 13 or hypodiploidy have a poor outcome. Interphase fluorescence *in situ* hybridization (FISH) detects del 13 in more patients than conventional cytogenetic markers.[22] Currently, there are no specific treatment guidelines for patients diagnosed to have del 13 at baseline.[20,22] Patients with good cytogenetic markers do well with high dose chemotherapy (HDCT) and autologous stem cell transplantation (ASCT).[23]

Proliferation as measured by the plasma cell labelling index (PCLI), β2 microglobulin or gene expression profiling (GEP) is another poor risk feature. GEP has been utilized (i) to identify high risk patients and (ii) to differentiate between normal plasma cells and those in MGUS, MM, AL amyloidosis and extramedullary plasmacytomas.[19,22]

PATHOGENESIS

MGUS is considered to be the initial event in the pathogenesis of myeloma. A multistep development model suggests that MGUS might progress to smoldering myeloma, and ultimately to

TABLE I. International Staging System (ISS) classification (adapted from reference 17)

Risk score	Serum albumin	Serum β2 microglobulin	Median survival (months)
Low	≥3.5 g/dl	3500 μg/L	62
Intermediate	Serum β2 microglobulin <3500 μg/L and serum albumin <3.5 g/dl or serum β2 microglobulin 3500–5500 μg/L		44
High	–	>5500 μg/L	29

symptomatic intramedullary and extramedullary myeloma or plasma cell leukaemia.[21,24,25]

The interaction of malignant plasma cells with the bone marrow microenvironment plays a key role in the pathogenesis of MM. The bone marrow microenvironment consists of haematopoietic progenitor and stem cells, immune cells, stroma cells, endothelial cells, osteoclasts and osteoblasts. In addition, there are non-cellular components such as collagen fibrils, fibronectin, laminin, proteoglycans, glycosaminoglycans and mineralized bone. The cellular and non-cellular components form a complex niche, where plasma cells expand. The direct interaction of plasma cells with these components and growth factors/cytokines secreted by either plasma cells or stromal cells or both, supports growth, survival, migration and confers drug resistance to the malignant plasma cells.[21,25] The key cytokines with antiapoptotic activity/proliferative activity include interleukin-6 (IL-6), insulin-like growth factor (IGF-1), vascular endothelial growth factor (VEGF), tumour necrosis factor-α (TNF-α), stroma derived growth factor-1α (SDF-1α) and B cell activating factor (BAFF). Thus, the plasma cell–bone marrow microenvironment interaction is a result of several signalling pathways that regulate critical components of plasma cell biology. In addition, mechanisms that involve DNA repair, chromatin structure, acetylation and de-acetylation of genes, and protein trafficking within the cytoplasm have been identified as other potential targets.

Bone lesions

The presence of osteolytic bone lesions is the hallmark of myeloma. These lesions are due to increased bone resorption. The central pathway in this process involves the receptor activator of nuclear factor kappa B (NFκB) (RANK); RANKL—the ligand for RANK and osteoprotegerin—a decoy receptor for RANKL. Osteoprotegerin prevents bone resorption by peventing binding of RANKL to RANK, thereby inhibiting the upregulation, proliferation and fusion of osteoclast precursors to produce mature osteoclasts. The increase in the ratio of RANKL to osteoprotegerin results in the activation of osteoclasts and bone resorption. Overexpression of RANKL is probably mediated in part by the release of macrophage inflammatory protein-1μ (MIP-1μ) by neoplastic plasma cells. The balance of bone resorption and formation is also affected by other systemic and local factors, e.g. glucocorticoids, 1,25-dihydroxyvitamin D3, parathyroid hormone, prostaglandins, cytokines including IL-1, -6, -11 and -17, and TNF.[21,25,26]

TREATMENT

All symptomatic patients should receive treatment. Patients who are asymptomatic or those with smoldering myeloma can be kept on close follow up. Initial supportive treatment includes adequate hydration, bisphosphonates, management of renal failure, correction of anaemia and control of infection.

The choice of initial therapy for patients of myeloma is based upon their eligibility for HDCT and ASCT, which in turn is based on their age, performance status and co-morbid conditions, e.g. cardiac and renal. Patients who are ≤65 years of age with no major co-morbid conditions are usually treated with induction therapy for 4–6 months followed by ASCT.

Induction therapy for patients eligible for ASCT

At present, a combination of immunomodulators (thalidomide or lenalidomide and dexamethasone) or proteasome inhibitors (bortezomib and dexamethasone) is used for induction. The overall response rate (complete and partial) with these combinations varies from 60% to 90%. These combinations are superior to 4-day continuous intravenous infusion of vincristine, adriamycin and oral dexamethasone pulse (VAD)[27] and vincristine, adriamycin and methyl prednisolone (VAMP)[28] in terms of response rates, ease of administration and efficacy for collection of stem cells.[29]

Immunomodulators

Thalidomide, lenalidomide and pomalidomide are the immunomodulators. Thalidomide and lenalidomide are approved for the treatment of relapse and primary treatment.[30,31] Pomalidomide is currently undergoing phase II trials.[32] These agents have immunomodulatory, anti-angiogenic and direct apoptotic properties. They inhibit growth of myeloma cells either through direct interference with key functions of MM cells or indirectly through modulation of signalling pathways that regulate their interaction with stromal cells of the bone marrow. Lenalidomide and pomalidomide are more potent than thalidomide.

The side-effects of thalidomide include somnolence, constipation (dose-related), neuropathy (related to dose and duration) and fatigue. The less common ones are oedema, venous thrombosis, skin rash, bradycardia (5%), neutropenia and hypothyroidism. The frequency of venous thrombosis is low when thalidomide is used alone (1%–3%) but is higher when combined with dexamethasone (10%–15%) or other cytotoxic agents, e.g. doxorubicin (25%). Thalidomide is a teratogenic drug and its use in pregnancy is contraindicated. In elderly patients the use of thalidomide may cause disturbing constipation and neuropathy.[33]

Lenalidomide, a thalidomide derivative, is free of somnolence, causes mild constipation and minimal neuropathy. However, it may be associated with myelosuppression and, therefore, needs close monitoring. Lenalidomide can be used with dose modification in patients with renal failure.[33]

A combination of lenalidomide and low dose dexamethasone (40 mg once a week) is the standard schedule.[34] There has been some concern about collection of progenitor cells after lenalidomide therapy[35] but this appears to be minimized if a combination of cyclophosphamide and a growth factor is used for mobilization.[36] At present, stem cell collection is usually done after 4 cycles of lenalidomide and dexamethasone (Table II).[37]

Proteasome inhibitors

Bortezomib is a selective and reversible inhibitor of 26S proteasome. Proteasome plays a role in the degradation of ubiquitinated proteins, which in turn have important functions in controlling tumour cell growth and survival. Bortezomib targets the myeloma cell and the bone marrow microenvironment by inhibiting the binding of myeloma cells to stromal cells and bone marrow triggered angiogenesis.[48] Carfilzomib and salinosporamide A are two other proteasome inhibitors currently under evaluation in phase I–II studies.[49] A combination of bortezomib with dexamethasone, doxorubicin, lenalidomide or thalidomide and melphalan has synergistic activity and may overcome resistance to either agent (Table III).[50–53] 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.[50] The pre-transplant use of bortezomib does not seem to have a negative impact on stem cell harvest or engraftment.

Therapy with bortezomib is associated with gastrointestinal (nausea/diarrhoea) toxicity, thrombocytopenia, peripheral neuropathy, fatigue and higher frequency of herpes zoster

TABLE II. Immunomodulators for newly diagnosed multiple myeloma: Phase III trials

Author (year)	Regimen	*n*	ORR (%)	Median PFS (months)	Median OS (months)
Rajkumar (2008)[38]	T/D *v.* D	470 (age 31–86 years)	63 *v.* 46; p<0.001	14.9 *v.* 6.5; p<0.001	na
Lokhorst (2008)[39]	TAD *v.* VAD	402 (age 18–65 years)	72 *v.* 54; p<0.001	Patients had transplant	na
Zervas (2007)[40]	VAD+Do *v.* VAD+T	232 (age <75 years)	63 *v.* 81*; p<0.003	45% *v.* 59%; p<0.013	65% *v.* 77%; p<0.037
Rajkumar (2006)[41]	T/D *v.* D	207	63 *v.* 41; p<0.0017	na	na
Hulin (2009)[42]	MPT *v.* MP+placebo	229 (age >75 years)	90 *v.* 39; p<0.001	24.1 *v.* 18.5; p<0.001	44 *v.* 29.1; p<0.02
Ludwig (2009)[43]	T/D *v.* MP	289 (all ages; not eligible for transplant)	68 *v.* 50; p<0.002	16.7 *v.* 20.7; p=0.2	41.5 *v.* 49.4; p<0.024
Palumbo (2008, 2006)[44,45]	MPT *v.* MP	255 (age 60–85 years)	76 *v.* 47.6	21.8 *v.* 14.5; p<0.004	45 *v.* 47.6; p=0.79
Facon (2007)[46]	MPT *v.* MP *v.* RI/Transplant	447 (age 65–75 years)	76 *v.* 35* *v.* 65	na	51.6 *v.* 33.2 *v.* 38.3; p<0.0006
Rajkumar (2008)[34]	Len/HD dexa *v.* Len/LD dexa	445	79 *v.* 68; p<0.008	19.1 *v.* 25.3; p<0.02	75 *v.* 87; p<0.0002
Gay (2009)[47]	BiRD *v.* RD; case matched	72 each	73.6 *v.* 33.3 (VGPR); p<0.001	48.3 *v.* 27.5; p=0.07	89% *v.* 73% at 3 years; p=0.17

ORR objective response rate (includes complete and partial response) PFS progression-free survival OS overall survival na not available T thalidomide D dexamethasone A doxorubicin V vincristine Do liposomal doxorubicin * patients underwent transplant after induction therapy M melphalan P prednisolone RI reduced intensity Len lenalidomide HD high dose LD low dose Bi clarithromycin R revlimid VGPR very good partial response

TABLE III. Bortezomib in untreated multiple myeloma: Phase III trials

Author (year)	Regimen	*n*	ORR (%)	Median PFS (months)	Median OS (months)
San Miguel (2008)[50]	Bortezomib+MP *v.* MP	682	70 *v.* 35; p<0.00001	na	HR 0.61; p<0.008
Mateos (2009) [51]	VMP *v.* VTP	260 (253); age >65 years	81 *v.* 79; p=ns	71% *v.* 61% at 2 years; p=ns	81% *v.* 84% at 2 years; p=ns
Rosinol (2009)[52]	TD *v.* VTD *v.* VBMCP/VBAD/Bortezomib	305 (299)	64 *v.* 82 *v.* 75; p=ns	na	na
Palumbo (2009) [53]	VMPT *v.* VMP±maintenance	511	86 *v.* 79 (PR); p<0.02	70% *v.* 58.2% at 2 years; p=ns	89.6% *v.* 80% at 2 years; p=ns

ORR objective response rate (includes complete and partial response) PFS progression-free survival OS overall survival M melphalan P prednisolone na not available HR hazard ratio V (velcade) bortezomib T thalidomide D dexamethasone A doxorubicin B BCNU C cyclophosphamide

infection.[54] Therefore, patients should receive acyclovir prophylaxis. Peripheral neuropathy due to bortezomib can be painful but is generally reversible; patients with prior peripheral neuropathy are at higher risk.

For patients with grade 1–2 neuropathy or neuropathic pain, the dose of bortezomib can be reduced to 1 mg/m^2 or even 0.7 mg/m^2. Dialysis may reduce the concentration of bortezomib, and it should be administered after dialysis.[33]

Thus, treatment with thalidomide, lenalidomide or bortezomib in combination with dexamethasone is associated with higher response rates. 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.[55]

Patients not eligible for ASCT

Patients >65 years of age or those who due to co-morbid conditions are not candidates for HDCT and ASCT can be started on a combination of melphalan, prednisolone (MP) and thalidomide (MPT) until a plateau in response is reached (usually 6–9 cycles). A randomized study by Palumbo *et al.*[44,45] showed that a combination of MPT is superior to MP in elderly patients in terms of response, and overall and event-free survival. Two more randomized trials have confirmed these findings.[42,46] A combination of VMP (bortezomib and MP) is better than MP for previously untreated patients who are not candidates for ASCT.[50] The estimated overall survival in the VMP arm was 83% at 30 months, compared with 68% in the MP group (p<0.008). A similar survival has been reported with other combinations, e.g. 80% at 2 years with the MPT regimen,[44,45] and 90% at 2 years with MP and lenalidomide.[56] However, no head-to-head comparison between various combinations has been done. Sensory neuropathy could be an important limitation of bortezomib in these elderly patients.[51,57] Once the maximum response is achieved (after 6–9 cycles of MPT or lenalidomide/dexamethasone or 4–6 cycles of bortezomib/dexamethasone or VMP) patients can be kept on observation.

CRITERIA FOR RESPONSE

With gradual improvement in the outcome of patients with myeloma, the definition of complete response (CR) has been revised in the past 2 decades. Gore *et al.* defined CR as the disappearance of the M protein component in serum and/or urine electrophoresis with ≤5% plasma cells on bone marrow aspiration.[58] Blade *et al.* for the European Group for Blood and Marrow Transplant (EBMT) re-classified CR as true CR if the M component was negative on immunofixation with a normal bone marrow evaluation. Patients with normal electrophoresis but positive immunofixation were considered as having near CR (n-CR).[59] In 2006, the International Myeloma Working Group (IMWG) developed the uniform response criteria.[60] The additional features (over the EBMT response criteria) include the use of FLC ratio in the CR category and progression criteria for patients without measurable disease, addition of very good partial response (VGPR) and stringent response categories, elimination of minor response category and elimination of the mandatory 6-week wait time to confirm response (Table IV).[18]

HIGH DOSE CHEMOTHERAPY AND STEM CELL TRANSPLANT

During the past decade, a number of randomized and non-randomized studies have shown that treatment with high dose melphalan (200 mg/m^2) followed by ASCT is associated with CR rates of 40%–50% with improved overall and event-free survival. Data from randomized studies[61–66] have been summarized earlier.[6] Experience from our centre has been reported recently.[67] A higher CR rate achieved with ASCT is possibly the main mechanism responsible for superior outcome with ASCT.[68,69] Data on the effectiveness of ASCT in patients >65 years of age and those with end-stage renal disease is limited. Higher VGPRs and CRs obtained with newer molecules (thalidomide, lenalidomide and bortezomib-based combinations) have led to the debate whether ASCT could be mitigated.[70] It is possible that consolidation with ASCT is likely to sustain these responses for longer periods.

Double or tandem transplant

Barlogie *et al*.[71] developed the concept of a second ASCT within 1–6 months of recovery from the first transplant to improve the CR rates and survival. Non-randomized studies from their group and others reported a higher CR rate, and improved overall and event-free survival with double transplant. Attal *et al*. for the French Group reported results of the first randomized trial; overall and event-free survival was superior with double transplant compared with a single transplant.[72] In this study, patients with less than VGPR (<90% response) benefited more from a second transplant; overall survival of 11% at 7 years in the group receiving single *v.* 43% in the group receiving double transplant ($p<0.001$). The benefit was not so significant ($p=0.70$) among patients who had VGPR (≥90% response) or CR after the first transplant.[72]

Kumar *et al.* have recently reported the results of a meta-analysis of 6 randomized trials. The response rate was significantly better with double transplant (risk ratio 0.79, 95% CI 0.67–0.93) but with significantly higher mortality (risk ratio 0.79, 95% CI 1.05–2.79). The overall survival was not improved for patients treated with tandem transplants.[73] Thus, presently, double transplant should be considered as an experimental approach for younger patients who achieve less than VGPR with the first transplant or have high risk features.

Allogeneic BMT

This has the potential to eradicate the myeloma clone due to graft *v.* myeloma effect. However, the role of conventional allogeneic BMT in myeloma remains limited due to (i) high transplant-related mortality from severe graft *v.* host disease (GVHD), (ii) availability of HLA-identical sibling donor in only one-third of patients, and (iii) older age (median age at diagnosis 55–58 years).[6] During the past decade, a number of studies have explored the role of non-myeloablative (mini-transplant or reduced intensity) allogeneic transplantation from an HLA-identical sibling donor.[74–77] ASCT followed by mini allo-transplants is associated with a decreased risk of acute and chronic GVHD resulting in reduced transplant-related mortality (15%–20%). This approach allows transplants even for patients up to 65 years of age.

Donor lymphocyte infusions (DLI) have been shown to be effective in the treatment of relapsed myeloma after allogeneic SCT. Molecular CR can be obtained in a higher proportion of patients who have clinical CR after allogeneic transplantation.[78]

Thus, the high morbidity (acute and chronic GVHD) and mortality associated with allogeneic SCT precludes its routine use and presently this treatment must be considered experimental. However, by virtue of the graft *v.* myeloma effect, allogeneic transplant results in curing some patients and may be worth considering in young patients with high risk myeloma who have an HLA-identical sibling donor.[6]

Maintenance therapy

To improve progression-free and overall survival, a number of non-randomized and randomized studies have explored the role of maintenance therapy after induction therapy and/or ASCT. Interferon-α and steroids (prednisolone or dexamethasone) with or without thalidomide have been used. Maintenance with interferon-α was associated with a modest benefit in progression-free survival but minimal improvement in overall survival.[79] In view of the toxicity, cost and minimal survival benefit, it is no longer used. A randomized study compared 10 mg *v.* 50 mg oral prednisolone given on alternate days. There was significant improvement in the overall and event-free survival in the group receiving 50 mg prednisolone. However, the side-effects of long term steroid therapy preclude its routine use.[80] The results of 3 randomized studies using thalidomide showed improved event-

TABLE IV. Response definitions: European Group for Blood and Marrow Transplantation (EBMT) criteria (adapted from reference 59)

Complete response
Absence of M protein in serum and urine, as confirmed by immunofixation in 2 samples 6 weeks apart and <5% bone marrow plasma cells, no increase in size or number of osteolytic bone lesions and the disappearance of soft tissue plasmacytomas.

Partial responsee
≥50% reduction in the level of M protein in serum and a reduction in urine of at least 90% maintained for a minimum of 6 weeks; ≥50% reduction in the size of soft tissue plasmacytomas; no increase in size or number of lytic bone lesions; and for patients with non-secretory myeloma only: ≥50% reduction in plasma cells in a bone marrow aspirate and on trephine biopsy, maintained for a minimum of 6 weeks.

Near-complete response
Same criteria as for complete response but with a positive immunofixation test.

Very good partial response: More than 90% decrease in M protein

Minimal or minor response: Less than 50% decrease in M protein

Stable disease: Myeloma that has not responded but has not progressed

Progressive disease: Any of the following:

1. An absolute increase of more than 500 mg/dl of serum M protein, as compared with the nadir value; or
2. An absolute increase of more than 200 mg of urinary M protein in 24 hours;
3. A new bone lesion or plasmacytoma; or
4. An increase in the size of such lesions; or
5. Development of hypercalcaemia (serum calcium >11.5 mg/dl (2.9 mmol/L)

free survival.[81–83] The overall survival was better in two studies[82,83] but grade 3–4 neuropathy (7%–27%) led to discontinuation of thalidomide in a proportion of patients. Low dose thalidomide (50 mg daily) may be used in patients who achieve CR or VGPR after transplant and it is likely to have a lower risk of neuropathy. Recently, lenalidomide and bortezomib are being assessed for their role in maintenance.[84]

NEWER AGENTS

With better understanding of the biology of myeloma, a number of new targets and molecules blocking these targets have been identified. Two new drugs, pomalidomide and carfilzomib, have shown promise in phase II trials. These are likely to enter phase III trials soon and if the results are confirmed then these are likely to be incorporated in the first-line treatment of myeloma. Among other smaller molecules, monoclonal antibodies, particularly anti-IL-6 antibodies and histone de-acetylase inhibitors have shown promise in phase I and II trials.

Relapsed/refractory myeloma

Effective management of relapsed/refractory disease incorporates several different strategies depending on the prior treatment, response, and duration of response, as well as residual toxicity, age and physical condition. High dose dexamethasone[85] has a role in the management of disease complications such as cytopenias, renal impairment or spinal cord compression until another agent is added. Thalidomide–dexamethasone (Thal/dexa), lenalidomide–dexamethasone (Len/dexa) and bortezomib–dexamethasone based combinations can be used for patients who relapse after MP/VAD chemotherapy.[86,87] Patients who have received one of these combinations in the past could be put on Len/dexa or another combination. A combination of liposomal doxorubicin (pegylated formulation, associated with reduced cardiac toxicity and alopecia) with bortezomib was associated with a higher response rate.[88] Lenalidomide is active in thalidomide- or bortezomib-pretreated patients. Bortezomib alone or in combination with dexamethasone is active in thalidomide/lenalidomide-pretreated patients. HDCT followed by ASCT may be considered for responders and can result in prolonged remission in 20%–25% of them. A second ASCT may be considered for selected patients who have a long term treatment-free interval (>3 years) after their first ASCT.[25] Young patients who relapse following ASCT can be considered for allogeneic SCT from an HLA-matched sibling donor using reduced intensity conditioning. It is important to identify a subgroup of patients with relapse who are asymptomatic (smouldering behaviour); such patients need not be given further chemotherapy until they are symptomatic.

SUPPORTIVE THERAPY

Bisphosphonates

All patients of myeloma with bone lesions are candidates for bisphosphonate therapy. Bisphosphonates inhibit bone resorption by inducing apoptosis of and inhibiting IL-6 production by osteoclasts. Other probable mechanisms include an effect on the marrow microenvironment and modulation of the immune function of gamma delta T cells. In general, bisphosphonates bind to the surface of damaged bone and inhibit ongoing bone destruction and this improves the chances of bone healing. Zoledronic acid is more potent than the earlier versions, e.g. pamidronic acid, and is given monthly as an infusion over 20–30 minutes for 6–9 months. Treatment can be continued for longer periods at longer intervals (once in 6 months) in patients with persistent bone disease or osteoporosis. Treatment should be resumed in case of disease progression or relapse. Prolonged therapy may be associated with osteonecrosis of the jaw (more in patients with poor dental hygiene), and therefore unnecessary treatment in asymptomatic patients must be avoided. Similarly, the dose of zoledronic acid must be reduced in patients with renal failure and should be avoided in patients with serum creatinine >3 mg/dl.[89] Patients with persistent localized bone pain can benefit from local radiotherapy (8 Gy single fraction) and vertebroplasty. The latter provides local pain relief and bone strengthening, and can be an option in patients with vertebral collapse but it does not restore vertebral height.[90]

Anaemia

The aetiology of anaemia in myeloma is multifactorial. Inadequate levels of erythropoietin (EPO) (present in up to 50%), anaemia of chronic disease, iron and vitamin B_{12} deficiency are important factors.[91] Following response to antimyeloma therapy, anaemia responds in most patients. Replacement therapy with recombinant EPO is a useful adjuvant and has been shown to be effective in 80% of patients with a mean haemoglobin increase of >2 g/dl. EPO can be started when the haemoglobin is <9 g/dl and the dose should be adjusted to maintain the haemoglobin at 11–12 g/dl. It is given in a dose of 100 units/kg 2–3 times a week or 30 000–40 000 i.u. per week or 2.25 mg/kg darbopoietin per week subcutaneously (SC). If after 2 weeks of therapy, the serum EPO levels exceed 100 mU/ml and the haemoglobin does not increase by at least by 0.5 g/dl, a lack of response can be predicted with 93% accuracy. In the absence of serum EPO measurements, serum ferritin can be done to predict the outcome. Patients with low serum ferritin levels (<400 ng/ml) are likely to respond to treatment.[92] Before starting a patient on EPO, it is important to correct iron, folic acid and vitamin B_{12} deficiency, if present. Continuing EPO in patients with a haemoglobin of >12 g/dl, increases the risk of thrombosis.[21,43]

Infections

Many patients with myeloma develop bacterial infections. This increased susceptibility is due to hypogammaglobulinaemia, granulocytopenia and low cell-mediated immunity. Gram-positive (e.g. *Streptococcus pneumoniae, Staphylococcus aureus* and *Haemophilus influenzae*) and Gram-negative (*Pseudomonas aeruginosa*) organisms are the common pathogens.[21,92] Patients receiving dexamethasone should receive trimethoprim–sulphamethoxazole prophylaxis. Similarly, patients on bortezomib therapy should receive herpes zoster prophylaxis.[42,92] Intravenous immunoglobulin may be considered as an adjuvant in patients with serious infections and hypogammaglobulinaemia. Nephrotoxic antibiotics, e.g. aminoglycosides should be avoided in patients with compromised renal functions.[21,33]

Renal failure

About 20%–25% of patients have renal dysfunction at the time of diagnosis. Myeloma kidney or cast nephropathy (80%), light chain deposition (5%–6%) and amyloidosis (<10%) are the main causes of renal failure. Dehydration, hypercalcaemia, hyperuricaemia, infections and the use of nephrotoxic drugs (e.g. aminoglycosides and non-steroidal anti-inflammatory agents) are reversible precipitating factors and should be corrected.[6] Dexamethasone alone or bortezomib, or bortezomib with dexamethasone with/without doxorubicin, or thalidomide with dexamethasone or VAD are preferred in patients with renal failure. Alkaline diuresis can reverse acute renal failure due to cast nephropathy.[21]

Venous thromboembolism (VTE)

VTE at initial presentation is uncommon but can occur in 3%–10% of patients receiving therapy with thalidomide plus dexamethasone and/or doxorubicin. Compared with thalidomide, the risk of VTE is low with lenalidomide and low dose dexamethasone (40 mg weekly). Recently, in a consensus paper, IMWG has recommended tailoring thromboprophylaxis according to risk factors. These include individual risk factors (age, obesity, history of VTE, central venous catheter, co-morbid conditions such as cardiac disease, chronic renal disease, diabetes, infections, immobilization, surgical procedures and inherited thrombophilia), myeloma-related risk factors (hyperviscosity) and therapy-related risk factors (high dose dexamethasone, doxorubicin or multiagent chemotherapy). It is recommended to give aspirin (75–100 mg) to patients with no or one risk factor (individual or myeloma related). Low molecular weight heparin (LMWH) or full dose warfarin is preferred for patients with at least 2 individual or myeloma-related risk factors and for all patients receiving high dose dexamethasone, doxorubicin or multiagent chemotherapy, regardless of the presence of additional risk factors. The duration of prophylaxis is 4–6 months. For patients who experience VTE during treatment, those who were previously on aspirin should receive LMWH and for those on LMWH prophylaxis, should be switched to therapeutic doses. Prophylaxis can be restarted after 6 months of anticoagulation.[33,93]

CONCLUSION

The management of myeloma has evolved over the past 2 decades. From being incurable the disease is now a chronic illness. Initial induction therapy followed by consolidation with intensive chemotherapy and ASCT is the preferred treatment for younger patients without major co-morbid conditions and is associated with a higher CR and improved event-free survival. The role of maintenance therapy after ASCT is currently under evaluation. The availability of newer drugs (thalidomide, lenalidomide, bortezomib and liposomal doxorubicin) has provided an opportunity to achieve higher response rates (translating into survival benefit) and to tailor therapy in an individual patient (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 VTE bortezomib-based regimens can be used safely).[94] Treatment with lenalidomide or bortezomib for patients with poor cytogenetics (chromosome deletion t(4;14), t(14;16), 17p–) appears to result in an outcome similar to that in patients without these abnormalities.[21] For elderly patients or those with major co-morbid conditions, both lenalidomide and bortezomib can be used after appropriate dose modifications.[33]

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