REVIEW ARTICLE

Drugs 1999 Apr; 57 (4): 485-506
0012-6667/99/0004-0485/$22.00/0

Current Drug Therapy for Multiple Myeloma

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Abstract

Recent years have witnessed tremendous advances in the molecular pathogenesis and management of multiple myeloma. Standard chemotherapy (melphalan and prednisone; MP) has been the mainstay of treatment of multiple myeloma for about 3 decades. However, it is no longer considered the 'gold standard', particularly for those patients who will subsequently undergo intensive chemotherapy with autologous or allogeneic peripheral blood stem cell (PBSC) or bone marrow transplantation (BMT), or for patients with refractory myeloma. A variety of induction combination chemotherapy regimens have been developed, some of which have demonstrated an improved response rate and duration and a superior 5-year survival rate when compared with standard chemotherapy. The early use of high dose chemotherapy with autologous PBSC support or BMT has significantly increased the complete remission rate, and has prolonged event-free sur-

vival and overall survival. Allogeneic bone marrow or PBSC transplantation may be a good option for selected patients with poor prognostic features.

The role of interferon-α in multiple myeloma is still inconclusive despite many years of clinical evaluation. The clinical application of chemosensitising agents that can inhibit P-glycoprotein (P-gp) expression and function, and particularly the development of more potent P-gp modulators such as valspodar (PSC 833) and elacridar (GF120918) has made it possible to reverse multidrug resistance in some refractory patients and to enhance the efficacy of chemotherapeutic agents. Immunotherapeutic approaches to purging of autologous bone marrow or PBSC, or as adjuvant therapy for minimal residual disease, show great promise. Finally, a number of new therapies specifically designed to treat many of the complications of multiple myeloma are improving clinical outcomes and quality of life for these patients.

Multiple myeloma (MM) accounts for approximately 10% of all haematological malignancies in the United States. For reasons that are poorly understood, it occurs twice as frequently in Blacks than in Whites.[1] It is considered a disease of older adults, presenting most commonly in individuals aged over 50 years, with a median age of 70 for women and 68 for men.[2] In 1998 an estimated 13 800 new cases will be diagnosed and 11 300 patients will die from this disease.[3]

MM is one of several diseases that have been collectively termed plasma cell dyscrasias. Pathologically, these disorders have as their common denominator abnormal growth and/or dysregulation of plasma cells and plasmacytoid cells. MM results from the clonal proliferation of plasma cells and clinically presents most frequently with renal insufficiency, recurrent bacterial infections, lytic bone lesions, hypercalcaemia and anaemia.[2] There is almost always a monoclonal immunoglobulin (Ig) present in the serum and/or urine, generally of the IgG or IgA class. When a monoclonal protein is present in the absence of MM or other related plasma cell dyscrasias, such as amyloidosis or macroglobulinaemia, it is termed a monoclonal gammopathy of undetermined significance. Approximately 3% of normal individuals over the age of 70 have a monoclonal protein in the serum, but the majority never develop MM and do not require therapy. However, approximately 16% will develop the disease eventually, and therefore close follow up of these individuals is mandatory.[4]

Recent advances in MM biology have increased our understanding of the pathogenesis of MM and provided new rationale for the development of novel therapies. It is believed that the development of MM may proceed via a multistep transformation process which involves a series of molecular events, including gene mutation, oncogene activation and growth factor dysregulation.[5] The presence of somatic mutations in the Ig genes of myeloma cells indicates that the oncogenic events specific for the emergence of myeloma clones occur late in B-cell development, probably in a plasmablastic cell or memory B cell.[6,7]

A number of studies have demonstrated that interleukin-6 (IL-6) is a major cytokine in regulating the growth and survival of myeloma cells.[8] It supports tumour cell growth and prevents apoptosis of these cells induced by a variety of agents such as dexamethasone or anti-Fas antibody.[5,9,10] Elevated serum IL-6 levels also contribute to many of its symptomatic features such as anaemia, thrombocytopenia, elevated acute phase proteins and bone lesions.[8] In the majority of cases, the production of IL-6 is by a paracrine mechanism from the tumour microenvironment in the marrow rather than by an autocrine loop.[11,12] IL-6 can also bind to a circulating soluble IL-6 receptor molecule (sIL-6R) and signal the cells through a signal transducer gp130, even though the cells are not producing the membrane bound IL-6R.[8]

More recently, Kaposi's sarcoma-associated herpes virus (KSHV) has been implicated in the

development of myeloma, possibly through alterations in the bone marrow microenvironment and production of viral IL-6.[13-16] However, the precise role of KSHV in the evolution of myeloma still needs to be defined.

1. Diagnosis, Staging and Prognosis Factors

A number of criteria have been developed to standardise the diagnosis of MM and to distinguish it from related entities (table I). Once the diagnosis of myeloma is suspected, an initial evaluation should include a complete blood count, blood chemistries (BUN, creatinine, calcium), serum electrophoresis, immunofixation or immunoelectrophoresis to define the Ig isotype, 24 hour urine protein electrophoresis, quantitative Igs, skeletal bone survey and bone marrow aspiration and biopsy. Some individuals have a form of myeloma that is associated with few symptoms, or associated problems such as renal insufficiency or anaemia, and have been classified as having indolent or smouldering myeloma (table II). They do not require therapy until progressive disease develops.[18,19]

Table I. Criteria for diagnosis of multiple myeloma[17-19]

Major criteria
1. Plasmacytomas on tissue biopsy
2. Bone marrow plasmacytosis (>30% plasma cells)
3. Monoclonal immunoglobulin spike on serum electrophoresis IgG >3.5 g/dl or IgA >2.0 g/dl; kappa or lambda light chain excretion >1 g/day on 24h urine protein electrophoresis
Minor Criteria:
a. Bone marrow plasmacytosis (10 to 30% plasma cells)
b. Monoclonal immunoglobulin present but of lesser magnitude than given above
c. Lytic bone lesions
d. Normal IgM <50 mg/dl, IgA <100 mg/dL or IgG <600 mg/dl
Any of the following sets of criteria will confirm the diagnosis:
Any 2 major criteria
Major criterion 1 plus minor criterion b, c or d
Major criterion 3 plus minor criterion a or c
Minor criteria a, b and c or a, b, and d

Table II. Diagnosis of indolent and smouldering myeloma[17-19]

Indolent myeloma (same as myeloma except:)
No bone lesions or <3 lytic lesions. No compression fractures
M-component levels: (a) IgG < 7 g/dL; (b) IgA <5 g/dL
No symptoms or associated disease features
performance status >70%
haemoglobin >10 g/dL
serum calcium normal
serum creatinine <2 mg/dL
No infections
Smouldering myeloma (same as indolent myeloma except:)
No bone lesions
Bone marrow plasma cells ≤30%

Several staging systems have been devised for MM, but the Durie-Salmon system is most commonly used (table III).[20] It is a loose approximation of tumour load and is correlated with survival time. Overall median survival is approximately 2.5 to 3 years, but patients with stage III disease and adverse prognostic markers do substantially worse. Renal function, which is included in this staging system, is a powerful prognostic feature, with azotemia being independently associated with shorter survival time.[21] Most patients with MM die of infection and/or renal failure.

In addition to the Durie-Salmon staging system, other prognostic factors have been identified. β2-microglobulin is considered one of the most powerful prognostic indicators.[21,22] However, in the presence of renal failure it may not be useful, since it is renally excreted. Bone marrow plasma cell labelling index is also an important prognostic indicator, but unlike β2 microglobulin it is not a readily available test.[22,23]

A large number of other prognostic markers have been described in an attempt to identify high risk patients for whom aggressive or experimental therapy is warranted. They include lactate dehydrogenase (LDH),[24] C-reactive protein (CRP),[25] morphology,[26] karyotype,[27] cell surface phenotype,[28,29] interleukin-2 (IL-2),[30] IL-6 levels[31] and, most recently, soluble IL-6 receptor.[32] It is possible that some of these markers may also become useful therapeutically. For example, prelim-

inary studies[33] utilising monoclonal antibodies (MAbs) against IL-6 *in vivo* have shown inhibition of myeloma cell growth. Patients with normal cytogenetics survived for significantly longer than those with abnormal chromosomes.[34-36] In a study[25,37] with 496 patients, a particularly poor outcome (shorter survival time) was observed in patients with chromosal translocations and those with 11/13 chromosome abnormalities, despite autologous bone marrow transplantation (BMT).

2. Treatment Options

2.1 Standard Chemotherapy

Oral administration of melphalan and prednisone has remained a standard form of therapy in the treatment of MM for almost 30 years (table IV). This regimen consists of melphalan 9 mg/m^2 and prednisone 100mg administered on days 1 to 4 with repeated courses at 4 to 6 week intervals for at least 1 year.[38,39] These agents can then be discontinued if the monoclonal Ig levels measured in either serum or urine have been stable for at least 6 months (plateau phase). Numerous prospective trials[38,40] have demonstrated that treatment with this regimen yields a response rate of about 50% with few complete remissions (CR, <5%), an average remission duration of approximately 18 months and a median survival of 24 to 30 months. The reported 5-year survival rate is less than 20%.[41]

Failure to respond to melphalan may be secondary to variable individual absorption and differences in cell sensitivity to the drug, and dose escalation may be necessary.[39,42-45] Furthermore, treatment with melphalan or other alkylating agents is leukaemogenic and may result in acute myeloid leukaemia in up to 20% of 4-year survivors.[46,47]

Regimens substituting cyclophosphamide for melphalan have also been used (table IV), as cyclophosphamide is less toxic to bone marrow and can be used more readily in patients with impaired renal function, granulocytopenia and thrombocytopenia.[48]

Most regimens used in the treatment of MM include corticosteroids, which are beneficial in increasing response rates when combined with cytotoxic drugs, and may prolong survival.[56] In one recently completed Southwest Oncology Group study,[56] the effect of corticosteroid dose was evaluated during induction therapy with VMCP/VBAP (vincristine, melphalan, cyclophosphamide and prednisone alternating with vincristine, carmustine, doxorubicin and prednisone) and VAD (vincristine, doxorubicin and dexamethasone); the dose of corticosteroid was found to play an important role in achieving higher remission rates and in prolonged median survival. In fact, initial therapy with dexamethasone alone has been shown to produce response rates similar to those achieved by treatment with standard chemotherapy (melphalan and prednisone; MP) or a VAD regimen.[57] High dose corticosteroids are especially useful in the management of patients with pathological spine fractures and cord compression, and in limiting severe myelosuppression.[58]

Table III. Staging system for multiple myeloma[20]

Stage I
All of the following:
Haemoglobin >10 g/dl
Serum calcium <12 mg/dl
Normal bones on radiographs, or solitary plasmacytoma
Low M-component
IgG <5 g/dl
IgA <3 g/dl
Urine light chain <4 g/24h
Stage II
Fitting neither stage I nor III
Stage III
More than one of the following:
Haemoglobin <8.5 g/dL
Serum calcium >12 mg/dl
Advanced lytic bone lesions
High M-component
IgG >7 g/dl
IgA >5 g/dl
Urinary light chain excretion >12 g/24h
Subclassification
A - serum creatinine <2.0 mg/dl
B - serum creatinine ≥2.0 mg/dl

Table IV. Common regimens used in the induction therapy

Regimen	Drugs	Dosage	Cycle (weeks)	References
VAD	VCR	0.4 mg/d IV by CI d 1-4	4	39
	DOX	9 mg/m^2/d IV by CI d 1-4		
	DEX	40 mg/d PO d 1-4, d 9-12, d 17-20		
MP	M	9mg/m^2 d 1-4	4-6	48
	P	100mg d 1-4		
CP	CTX	1000 mg/m^2 IV d 1	3	48
	P	100mg d 1-4	3	
CP	CTX	300 mg/m^2 IV d1	1	48
	P	100mg PO d 1-2		
VAMP	VCR	0.4mg IV by CI d 1-4	3-4	48
	DOX	9 mg/m^2 IV by CI d 1-4		
	Methyl-P	1.5g IV d 1		
HDMP	M	140 mg/m^2 IV by CI d 1	3-4	48
	Methyl-P	1000mg IV or PO d 2-6		
M-2 protocol	VCR	1.2 mg/m^2 (max 2mg) IV d 1	5	49
(VBMCP)	BCNU	20 mg/m^2 IV d 1		
	M	8 mg/m^2 PO d 1-4		
	CTX	400 mg/m^2 IV d 1		
	P	40 mg/m^2 PO d 1-7 (all cycles), 20 mg/m^2 on d 8-14 (during first 3 cycles only)		
VMCP/VBAP	VCR	1 mg/m^2 IV d1 (1.5mg max)	3	50, 51
	M	6 mg/m^2 PO d 1-4		
	CTX	125 mg/m^2 PO d 1-4		
	P	60 mg/m^2 PO d 1-4		
	alternated with			
	VCR	1 mg/m^2 IV d 1 (1.5 mg max)	3	
	BCNU	30 mg/m^2 IV d 1		
	DOX	30 mg/m^2 IV d 1		
	P	60 mg/m^2 PO d 1-4		
ABCM	DOX	30 mg/m^2 IV d 1	6	52
	BCNU	30 mg/m^2 IV d 1		
	CTX	100 mg/m^2 d 22-25		
	M	6mg/m^2 d 22-25		
DC-IE	DEX	40 mg/d PO d 1-4	3	53
	CTX	1000 mg/m^2 IV d 5		
	Idarubicin	5 mg/m^2 IV d 8-10		
	Etoposide	100 mg/m^2 IV by CI q 12h, d 8-10		
CyE	CTX	600 mg/m^2 IV d 1-5	3	54
	Etoposide	180mg IV d 1-5		
EDAP	Etoposide	1200 mg/m^2 IV by CI d 1-4	3-4	55
	DEX	40 mg/m^2 IV or PO d 1-5		
	Ara-C	1000 mg/m^2 IV d 5		
	Cisplatin	20 mg/m^2 IV by CI d 1-4		
DEX	DEX	20 mg/m^2 d 1-4, d 9-12, d 17-20	5	57

Ara-C = cytarabine; **BCNU** = carmustine; **CI** = continuous infusion in a central vein; **CTX** = cyclophosphamide; **d** = day; **DEX** = dexamethasone; **DOX** = doxorubicin; **IV** = intravenously; **M** = melaphalan; **methyl-P** = methylprednisone; **P** = prednisone; **PO** = orally; **VCR** = vincristine.

2.2 Combination Chemotherapy

Because of the modest success attained using standard chemotherapy, a variety of regimens using multiple chemotherapeutic agents have been studied for use as both first- and second-line agents (table IV). Combination chemotherapy, introduced in the 1970s, arose from the observation that both murine and human plasmacytomas which were resistant to melphalan were sensitive to cyclophosphamide.[39] One of the best known of these regimens is the M-2 protocol (VBMCP), devised at Memorial Sloan-Kettering Cancer Center in 1977. This regimen consisted of vincristine, the nitrosourea carmustine (BCNU), melphalan, cyclophosphamide and prednisone, and was associated with a response rate of 78% and a median survival of 38 months.[59]

The Eastern Cooperative Oncology Group (ECOG)[49] conducted a large randomised study in which VBMCP was compared with treatment of MP, the results of which demonstrated that VBMCP induced a higher response rate (72% *vs* 51%), a longer response duration (median 24 *vs* 18 months) and a slightly higher 5-year survival rate (26% *vs* 19%), but no significant difference in overall survival (OS, 29 *vs* 27 months).

The VMCP/VBAP regimen was studied by the Southwest Oncology Group[50,60] and consisted of alternating 3-week cycles of vincristine, melphalan, cyclophosphamide and prednisone with vincristine, BCNU, doxorubicin and prednisone. This regimen resulted in a median survival of 30 months with a 5-year survival rate of 30%, but only a 54% response rate. The UK Medical Research Council (MRC)[52] studied a similar regimen, ABCM, consisting of doxorubicin, BCNU, cyclophosphamide and melphalan, and demonstrated a modestly increased 5-year survival rate compared with melphalan therapy.

Numerous other intensive first-line regimens have been devised for the treatment of MM, most of which have failed to offer significant increases in survival rates compared with standard treatment with melphalan and prednisone. The regimen consisting of vincristine, doxorubicin, and dexamethasone (VAD), and a similar combination containing high dose methylprednisone (VAMP), were shown to produce less bone marrow toxicity than other regimens containing alkylating agents, and were particularly notable for their rapid induction of remission.[58] These combinations have not been found to be superior to standard MP therapy when used as first line agents, but may have a role in the treatment of patients in whom autologous transplantation is anticipated, and in patients with refractory myeloma.[51,61]

The controversy regarding whether MP or combination chemotherapy should be used as initial therapy for multiple myeloma has not been resolved. Combination chemotherapy does appear to offer higher response rates and slightly higher 5-year survival rates for those patients who can tolerate these intensive regimens. One study[62] in 1992 examined 18 randomised controlled trials comparing standard chemotherapy with different combined regimens, and concluded that there was no significant difference in 2-year survival rates. However, the study did not examine possible differences in long term survival in certain subsets of patients.

2.3 Maintenance Chemotherapy

Maintenance therapy for myeloma entails chemotherapy given after patients have reached a maximal response and entered a plateau phase.[63] MP has been evaluated as maintenance therapy in 3 different trials, with no resultant increased survival reported.[63] In addition, continuing use of an alkylating agent increases the risk of developing myelodysplasias and acute leukaemias. One Italian study has reported that use of interferon-α (IFNα) as maintenance therapy may prolong the plateau phase.[64] However, a subsequent Australian study concluded that while maintenance therapy with IFNα may prolong the plateau phase, no improvement in survival was shown when compared to no maintenance therapy.[65] In addition, long term IFNα use is associated with numerous adverse effects which may be intolerable to elderly patients. Therefore, continuation of cytotoxic chemother-

apy and/or IFNα appears to offer no benefit over observation alone with reinstitution of therapy at the time of clinical relapse. However, recent clinical studies suggest that early high dose chemotherapy with marrow or peripheral stem cell support, perhaps with a double autotransplant after initial induction, may prolong the response duration and overall survival of younger patients who can tolerate this procedure.[66]

2.4 Refractory or Relapsing Myeloma

Patients who relapse later than 6 months after stopping initial therapy have a 60 to 70% chance of responding to re-initiation of the previously used induction therapy.[67] If no response ensues, then treatment with VAD or other regimens may be attempted. Both VAD and treatment with high dose dexamethasone have induced remissions in approximately 25% of patients with disease resistant to initial treatment, and have prolonged survival by 1 year in patients who responded.[68,69] Patients who relapse within 6 months of initial treatment have a 75% response rate to VAD.[68,70,71]

Responses to VAD are often seen rapidly, usually within the first 2 cycles of therapy. Clinical improvement is manifested via increased haemoglobin levels, decreased bone pain and improved performance status. The major adverse effects of VAD therapy are susceptibility to infection and gastrointestinal toxicity. While there are still concerns regarding the cost, adverse effects and efficacy of VAD for refractory myeloma, this regimen remains one of the best available treatments for these patients.

Several salvage regimens are available for patients with VAD resistance. One such regimen utilises etoposide, cisplatin, cytarabine and dexamethasone. This regimen has a response rate of 40%, but a median survival of only 4.5 months.[55] Another regimen (DC-IE; dexamethasone, cyclophosphamide, idarubicin, etoposide) yielded a 62% response rate in 24 relapsed or refractory patients with a median survival of 22 months for those who received high dose chemotherapy with autologous peripheral blood stem cell (PBSC) support after DC-IE.[53] Other second line chemotherapeutic regimens include Cy-E (cyclophosphamide and etoposide)[54] and HDMP (melphalan and methylprednisone).[55]

Even if patients do respond to these regimens, the duration of response is often limited. Several studies have shown that primary refractory or relapsing patients may still respond to high dose chemotherapy, while patients who relapse following high dose therapy, and then respond to reinduction regimens like VAD or VAMP, can still benefit from a second cycle of high dose treatment.[72-74]

2.5 High Dose Chemotherapy

High dose chemotherapy with marrow or peripheral stem cell rescue after initial induction in younger patients has been actively investigated in the past few years. The Intergroupe Francais du Myelome (IFM) 90 trial[75] conducted from 1990 to 1993 compared conventional chemotherapy with high dose therapy, and demonstrated a significant improvement in response rate, event-free survival and overall survival in the high dose therapy group. The most common and effective protocol of high dose chemotherapy by far is melphalan at doses of 140 mg/m^2 or higher, either alone or in combination with total body irradiation (TBI).[72,76] Extensive studies[77-80] have shown that melphalan alone in high doses induced higher response rates (up to 84%) and CR rates (up to 30%), but also caused prolonged and severe myelosuppression. The addition of granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) to this regimen did not significantly reduce the associated morbidity and mortality.[81,82] Autologous stem cell transplantation accelerated the restoration of haematopoiesis after high dose melphalan and increased the CR rates to 30 to 50%.[83,84] The addition of TBI to high dose melphalan has not been demonstrated to be superior to melphalan alone.[72] Other alternative high dose chemotherapy regimens used in small clinical studies (table V), have shown promising results, but further randomised clinical trials are needed to confirm their efficacy.

The optimal timing for high dose chemotherapy still remains controversial.[72] Fermand et al.[89] reported that high dose chemotherapy administered either at diagnosis or to relapsed or refractory patients resulted in similar survival rates. Another study[90] also suggested that high dose therapy did not benefit either early chemosensitive patients or refractory disease treated for longer than 1 year, but that primary refractory myeloma within the first year after diagnosis benefited most from high dose therapy. However, several recent large clinical trials have indicated that early high dose therapy (within 12 months after initial induction treatment) improved the prognosis,[25] and that initial treatment with high dose therapy significantly increased overall survival.[91]

Studies[92-95] also suggest that MM patients with end-stage renal disease (ESRD), including those on dialysis, can still tolerate intensive myeloablative therapy without major toxicity because melphalan clearance is not significantly delayed with severe renal impairment. Indeed, a substantial number of patients with renal impairment experience improvement in renal function, and CR has been observed with comparable autograft-related mortality. Therefore, renal dysfunction should not disqualify patients from receiving high dose chemotherapy and autologous transplantation.

Table V. Common high dose chemotherapy regimens

Drug regimen	Drug(s)	Dosage	Reference
HDM	M	200 mg/m^2	25
HDM + TBI	M	140 mg/m^2	25
	TBI	850-1125 cGY	
HDM + CTX	M	200 mg/m^2	25
	CTX	120 mg/kg	
TBC	Thiotepa	750 mg/m^2	85
	Busulfan	10 mg/kg	
	CTX	120 mg/kg	
BC	Busulfan	14-16 mg/kg	86
	CTX	120 mg/kg	
C + TBI	CTX	120 mg/kg	87
	TBI	1400 cGy	
M + CB	M	90 mg/m^2	88
	CTX	120 mg/kg	
	Busulfan	16 mg/kg	

Ara-C = cytarabine; **BCNU** = carmustine; **CTX** = cyclophosphamide; **DOX** = doxorubicin; **HDM** = high dose melphalan; **M** = melphalan; **P** = prednisone; **TBI** = total body irradiation.

2.6 Bone Marrow or Peripheral Blood Stem Cell Transplantation

2.6.1 Allogeneic Transplantation

The use of high dose chemotherapy with haematopoietic stem cell support is a major advance in the treatment of MM. Stem cell support can be accomplished by using either bone marrow or PBSC from syngeneic, allogeneic or autologous donors. In syngeneic BMT, there is no graft-versus-host disease (GVHD) and also a lack of graft-versus-myeloma effect. Allogeneic BMT avoids the reinfusion of malignant cells and probably establishes a graft-versus-myeloma effect, but has increased morbidity and mortality due to infection, GVHD and regimen-related toxicity. This is particularly notable in patients who are heavily pretreated or have refractory disease.[96-98]

Transplant-related mortality is quite variable, ranging from 15 to 56%.[96,99] In the European Group for Blood and Marrow Transplantation (EBMT) registry study,[98,100,101] 162 patients received allogeneic transplants. The CR rate was 44% overall and 60% for assessable patients, with a median event-free survival (EFS) of 36 months. The OS rate was 32% at 4 years and 28% at 7 years. Six years after transplant, 34% of patients in CR remained disease-free. However, early toxicity (infection, GVHD, regimen-related effects) was high, with a mortality rate of approximately 40% within the first 6 months. Patients with chemosensitive disease, transplanted after first-line therapy and achieving CR after BMT, do best.[101]

The International Bone Marrow Transplant Registry (IBMTR)[102] reviewed 257 patients receiving human leukocyte antigen (HLA)-identical sibling transplants with a variety of conditioning regimens. The probability of survival was 53% at 6 months and 24% at 5 years. Eleven patients were alive at more than 5 years, with 7 in CR. Favourable prognostic features included Karnofsky performance scores above 70 and sensitive disease prior to transplant. The Societe Francaise de Greffe de

Moelle (SFGM)[103] also evaluated 137 patients with allogeneic BMT. The CR rate was 51% with a median EFS from BMT of 33.3 months for patients achieving CR. The 5-year OS from transplant and diagnosis was 28.4% and 41.7%, respectively, and the transplant-related mortality was 42%. Acute GVHD and achievement of CR post-transplant were the 2 significant factors for EFS and OS. In the University of Arkansas,[104] 97 patients underwent allogeneic BMT from matched sibling or unrelated donors between 1988 and 1996. The CR rate was 26% and the actuarial 3-year probabilities of OS, EFS, relapse and toxic death were 17.5%, 11.8%, 59.9% and 54.4%, respectively. Elevated LDH and TBI were strong negative factors affecting survival in this study.

In summary, allogeneic BMT produces an overall CR rate of 33% to 58%, and about 30 to 50% of those achieving CR remain disease-free 3 to 6 years after transplantation.[96] Patients under the age of 56 who have an HLA-identical sibling donor and do not respond to autotransplant should be evaluated for allogeneic BMT. Better control of GVHD by using T-cell depletion of allografts and immunosuppressive agents such as cyclosporin or methotrexate may further improve the clinical outcome.[105] Mobilised allogeneic PBSC instead of bone marrow has been used successfully in eligible patients with reduction of transplant-related mortality and comparable response rate.[106]

2.6.2 Autologous Transplantation

Since the majority of patients with myeloma are not eligible for allogeneic transplantation, high dose treatment regimens employing autologous sources of bone marrow or peripheral blood stem cells are currently the most promising form of treatment for this disease. The mortality and morbidity associated with this approach has been decreased substantially by the use of recombinant haematopoietic growth factors such as GM-CSF or G-CSF and mobilised PBSC. PBSC has less contamination with myeloma cells and produces faster haematopoietic and immune reconstitution than bone marrow, making high dose therapy better tolerated and more cost-effective than other approaches. Although it is becoming the main cell source for autologous stem cell rescue, its use has not led to an increase in the overall response rate or survival when compared with autologous BMT.[107-110]

Autologous stem cell transplantation is relatively well tolerated, with a mortality rate (as a result of toxicity) of 2 to 11%, and can be used in patients up to age 70 years. It does not need a compatible donor and is free of GVHD, but there is a risk of graft contamination with tumour cells. A registry study from EBMT[111] reported that in 907 patients who received autologous stem cell support, the post-treatment CR rate for all patients was 49% and median survival time from treatment was 41 months. The source of the graft, CD34-selection or tandem transplantation did not significantly affect overall survival. Significant prognostic factors were response to chemotherapy, 1 line of primary induction therapy, stage I or II disease at diagnosis, age less than 51, a non-TBI preparative regimen, IFNα maintenance treatment and the achievement of CR post treatment.

An updated analysis of the IFM 90 trial,[112] compared the outcomes of patients who received high dose chemotherapy and autologous stem cell transplantation to those who received conventional therapy, with a median follow-up of 60 months from diagnosis. It demonstrated that high dose chemotherapy had a much higher 6-year probability of EFS (24% *vs* 15%) and survival (43% *vs* 15%). Response to treatment was found to be the most important prognostic factor for survival. The 5-year post-diagnosis survival rate was 65% for patients achieving CR or a very good partial response, 37% for patients with a partial response and 23% for patients with a minimal response or with progressive disease.

Although the administration of intensive therapy has increased the response rate to chemotherapy, it is ultimately followed by relapse. One potential way of improving this response is to further increase the dose-intensity of these treatments by proceeding sequentially with 2 cycles of high dose therapy in so-called tandem transplantation.[113]

Jagannath et al.[114] reported that aggressive high dose chemotherapy (total therapy) with double autologous stem cell rescues, in 231 newly diagnosed patients up to age 70, yielded a superior combined CR plus PR rate (81%) and extended the median duration of EFS (42 months) and OS (65 months). Transplant-related mortality during the first 12 months after enrolment was 9%.

The largest experience in double transplants has been reported in 542 patients enrolled at the University of Arkansas.[115,116] 95% completed 1 transplant and 72% completed 2 transplants. The first cycle was melphalan 200 mg/m^2 while the second consisted of melphalan 200 mg/m^2 or 140 mg/m^2 plus TBI. The CR increased from 24% after 1 cycle to 43% after the second cycle. Patients with either primary refractory disease or relapsed refractory reached 11% and 14% CR rates, respectively. The EFS for the whole group was 26 months, with a median survival of 47 months. The treatment-related mortality was 7%. Low β_2-microglobulin (<2.5 mg/L) and CRP (<0.4 mg/dl) and normal cytogenetics were the most significant parameters associated with improved EFS and OS. This study also demonstrated marked extensions of both EFS (median 44 months) and OS (median >5.5 years), regardless of pretransplant risk features, when the first transplant was done within 12 months of initial treatment and the second transplant no more than 6 months later.

Furthermore, in a pair-mate analysis,[117] the outcomes of 116 previously untreated patients receiving tandem transplants were compared with those of the untreated patients receiving standard therapy according to Southwest Oncology Group (SWOG) trials, after matching for the major prognostic features (age, β_2-microglobulin and creatine). The study showed that the patients with tandem transplants had a much higher response rate (CR plus PR) (85 *vs* 52%) and longer median duration of EFS (49 *vs* 22 months) and OS (62+ *vs* 48 months) than that of patients with standard therapy.

An ongoing IFM trial[118] is currently evaluating the role of single *vs* double transplantation. It has randomised a group of 400 previously untreated myeloma patients under the age of 60. Thus far, at 2 years of follow-up, no difference in overall response rate, EFS and OS has been demonstrated, but it may be premature to conclude that this approach is not beneficial, particularly for certain subgroups of patients. Longer follow-up and more randomised clinical trials are needed to determine the efficacy of this approach.

Further investigations into purging techniques to avoid contamination of the graft by myeloma cells, and treatment of minimal residual disease after autografting, are currently in progress. Anderson et al.[87,105] purged marrows with a combination of monoclonal antibodies (anti-CD10, CD20 and PCA-1) and complement in a series of 26 patients treated with cyclophosphamide and TBI conditioning regimen. The response rate and CR were 95 and 42%, respectively, with 36-month EFS. Reece et al.[88] reinfused marrow that had been treated *ex vivo* with 4-hydroxyperoxy-cyclophosphamide after a conditioning regimen with busulfan, cyclophosphamide and melphalan. The response rate was 78% with a CR of 57%, 17 month EFS and 17% toxic death rate. Schiller et al.[119] reported that CD34$^{+/-}$ selection of autografts resulted in a significant reduction of contaminating myeloma cells and produced durable neutrophil and platelet engraftment. However, the clinical impact of these novel clinical approaches needs to be further evaluated.

2.7 Interferon-α

The rationale for the clinical use of IFNα is based on the observation that IFNα inhibits the growth of myeloma cells *in vitro*, reduces the self-renewal capacity of myeloma stem cells and has a synergistic effect with cytotoxic agents.[8,120-122] The common dosage of IFNα used in MM is 2 MU/m^2 or 3 to 5 MU subcutaneously 3 times weekly.[76,123-125] It has been used as a single induction agent or in combination with conventional chemotherapy, in newly diagnosed MM or as maintenance therapy. However, the role of IFNα in the management of MM has still not been defined, despite extensive clinical evaluation in the last 2 de-

cades. When used as a single agent for initial therapy, IFNα has modest activity with an overall response in about 20 to 30% of patients that is clearly inferior to that of conventional chemotherapy.[8,126] The effectiveness of IFNα in combination with conventional chemotherapy for induction treatment is still controversial.

The Myeloma Group of Central Sweden[127] reported that the concomitant administration of IFNα with MP as initial treatment (MP/IFN) and then used as sole agent for maintenance therapy significantly increased response rate when compared with MP therapy alone, but did not prolong overall survival, except in patients with IgA or Bence-Jones myeloma. More recently, the Nordic Myeloma Study Group[125] published the results of a large randomised phase III clinical trial, which enrolled 592 newly diagnosed patients. Their study demonstrated that the addition of low dose IFN-α2b to standard MP therapy followed by IFN-α2b maintenance therapy does not improve response rate or survival, but the response duration and plateau phase duration are prolonged.

However, the Cancer and Leukaemia Group B Study[124] and Australia Leukaemia Study Group[128] failed to demonstrate an improvement in the response rate, duration of remission or survival when IFNα was combined with MP or combination chemotherapy. When used in relapsed or refractory diseases, IFNα also does not appear to show any benefit.[129,130]

The efficacy of IFNα for maintenance therapy also remains uncertain. Mandelli et al.[64] reported that maintenance treatment with IFNα after conventional chemotherapy significantly prolongs response and survival, while both the IFM and Canadian trials[123,131] showed that IFNα maintenance therapy improved the response duration, but that the difference in overall survival was of borderline significance. Westin et al.[132] also found that IFNα maintenance therapy increased the plateau phase duration with no effect on survival.

A pilot study done by Cunningham et al.[133] initially suggested that maintenance IFNα following high dose chemotherapy and autologous BMT prolongs both EFS and OS at median follow-up of 52 months. However, both EFS and OS has now ceased to be significant because most patients have ultimately succumbed to their disease. Studies done by the SWOG and German Myeloma Treatment Group,[56,134] in which maintenance therapy with IFNα was used, also did not prolong either response duration or survival.

Although most data from IFNα maintenance trials[128,135] show a prolongation of 5 to 13 months of relapse-free survival after achievement of response or plateau phase, it may negatively impact on the patient's quality of life; the use of IFNα may be associated with such adverse effects as fever, fatigue and myalgias. Therefore, the cost-benefit of this approach should be carefully evaluated. It has been suggested that IFNα be considered as maintenance therapy for selected patients who have responded favourably to initial therapy and who are expected to tolerate IFNα during long term therapy.[125]

2.8 Patient Characteristics Determining Treatment

One of the greatest challenges in treating patients with MM involves determining which treatment option is most appropriate for the individual patient. The results of the recent IFM trial[75] suggest that intensive therapy with high dose chemotherapy and stem cell transplant may be the treatment of choice for patients aged up to 65 years who have a good performance status, since even a prolonged survival of 4 to 5 years may be considered unacceptable in younger patients.[39] Induction therapy regimens without melphalan, such as dexamethasone, VAD or VAD-like, should be used for these patients because these regimens have no cross-resistance with melphalan and are much less toxic to marrow stem cells.[116] However, many older patients with concomitant illness may be unable to tolerate such intensive therapy, and conventional therapy may be the best option. MP should be considered in this situation because of its low cost and ease of administration.

The ideal treatment for patients aged 55 to 70 years has yet to be defined. ECOG[49] has recently reported that patients up to 70 years of age usually tolerated the VBMCP regimen well, with comparable toxicity when compared to MP, and had a higher response rate and longer response duration. More intensive regimens are appropriate for younger patients and, whenever possible, they should be considered for autologous or allogeneic transplants. Regimens without melphalan, such as VAD, may be preferable for patients with renal failure because drug excretion in the VAD protocol is predominantly nonrenal.[39] High dose dexamethasone treatment is suitable for patients with spinal cord compression who are on radiation therapy, or those with significant pancytopenia or hypercalcaemia.[39,57]

3. Management of Multiple Myeloma Complications

3.1 Bone Lesions and Hypercalcaemia

Bone destruction and hypercalcaemia are major clinical manifestations and a main cause of morbidity and mortality in patients with MM. More than 80% of patients at presentation have bone lesions, and the extent of the lesions is directly related to the mass of the tumour. About 30% of patients also have hypercalcaemia.[7,136] Bone lesions and hypercalcaemia are the consequence of excessive osteoclastic resorption and decreased bone formation, induced by the myeloma cells and tumour microenvironment through osteoclast-activating cytokines.[137]

Bisphosphonates (BPs) have demonstrated efficacy in reducing skeletal complications, preventing hypercalcaemia and improving survival in MM patients.[137,138] Three BPs have been evaluated in several large randomised clinical trials.[139-141] The Finnish Leukaemia Group[140] reported that oral clodronate (2400 mg/day for 24 months) reduced new osteolytic lesions by 50% in previously untreated patients, but did not affect bone pain or rates of pathological fracture. The MRC trial[142] also showed that clodronic acid (clodronate) significantly reduced new vertebral fractures after 1 year. The proportion of patients experiencing back pain or a decrease in performance status was significantly lower in the clodronic acid arm at the time of disease progression.

Another controlled, nonrandomised trial[143] with 341 newly diagnosed, untreated, consecutive patients found that when clodronic acid was administered at a dose of 600 to 1000 mg/day every 4 to 6 weeks intravenously, starting at diagnosis and continuing until death, the progression of skeletal disease occurred less often in patients who received the drug than in those who were not given prophylaxis (50 *vs* 34.8%). Survival was longer for patients on clodronic acid prophylaxis than those who did not receive clodronic acid prophylaxis.

One large study[139,144] consisted of 392 stage III patients who received either pamidronic acid (pamidronate) 90mg or placebo as a 4-hour infusion every 4 weeks for 21 cycles, in addition to chemotherapy. This study demonstrated that patients receiving pamidronic acid had significantly fewer skeletal complications. They experienced significant decreases in bone pain, had less analgesic drug use and had a better performance status than the placebo group. Although survival was not improved in patients receiving first-line chemotherapy, there was a significant survival advantage from 14 to 21 months in the group of patients where first-line chemotherapy had failed prior to entering the trial.

However, etidronic acid (etidronate) has failed to show significant clinical advantages in myeloma patients in two clinical trials.[145,146] The antiresorptive mechanism of BPs is thought to be through interference with the recruitment, differentiation and function of osteoclasts.[147] Some BPs may also have direct antitumour effects on myeloma cells by inducing cell cycle arrest and apoptosis of myeloma cells, and inhibiting IL-6 production from bone marrow stromal cells as shown in pamidronic acid and incadronic acid (incadronate) (YM175).[148,149] These beneficial effects suggest that the use of BPs prophylactically

to prevent the development of bone lesions in MM patients should become standard therapy.

Hydration, diuresis and corticosteroids have been the mainstays of treatment of hypercalcaemia in MM patients. Recently, BPs have become the treatment of choice for hypercalcaemia that persists after hydration and corticosteroids.[138] Both oral (800 to 3200 mg/day) and intravenous (100 to 600 mg/day) clodronic acid are effective in MM-induced hypercalcaemia.[138,150-152] The hypocalcaemic effect begins 2 to 3 days after initiation of therapy and normal values are reached in the majority of patients within 3 to 6 days. One single intravenous infusion (1500 mg/4h) was reported to be as effective as 300 mg/day intravenously for 5 days but it corrected hypercalcaemia more rapidly. A single slow infusion of 30 to 90mg of pamidronic acid corrected 90% of malignant hypercalcaemia with normacalcaemia reached within 4 to 6 days.[153,154] Etidronic acid was less effective than clodronic acid.[39]

Several more potent BPs, such as ibandronic acid and zoledronic acid, appear to be highly effective for tumour-induced hypercalcaemia. Regular intravenous injection or infusion of these drugs may lead to more marked and prolonged inhibition of bone resorption. Large multicentre trials of these 2 drugs are currently under way in myeloma bone diseases.[155,156]

A preliminary study[157] suggested that gallium nitrate could induce substantial pain relief and a marked reduction in the rate of bone loss in stable myeloma patients receiving chemotherapy. In 3 small, sequential, randomised trials,[158-161] it appeared to be more effective for the control of cancer-induced hypercalcaemia than calcitonin, etidronic acid or pamidronic acid. Further clinical evaluation is warranted. Gallium nitrate might exhibit its antiresorptive activity through inhibiting energy-dependent proton transport of osteoclast cells and by increasing new calcium accretion into bone matrix.[161] However, a serious adverse effect of this drug is nephrotoxicity, which may limit its usefulness.[162]

3.2 Anaemia

Anaemia is a common feature of multiple myeloma seen in at least two-thirds of patients at presentation. It is multifactorial in origin, including marrow replacement by the malignant cells, chronic renal failure, hyperviscosity, and chemotherapy- or cytokine-induced [IL-6, interleukin-1β (IL-1β) and TNF] marrow suppression. Many MM patients have inappropriately low levels of erythropoietin (EPO) for their degree of anaemia.[163] Treatment of the tumour burden with chemotherapy will increase haemoglobin levels in many patients. Data on the use of EPO have consistently demonstrated the role of this growth factor in ameliorating the degree of anaemia and improving the quality of life of MM patients who have severe or moderate anaemia.[164] Most responses occur within 2 months after initiation of treatment.

The Epoetin-alfa Multiple Myeloma Study Group[163] recently reported a placebo-controlled randomised study showing that EPO is a well tolerated and effective treatment for reducing transfusion needs and correcting anaemia associated with MM in patients on chemotherapy. 132 patients with a baseline haemoglobin (Hb) <11 g/dl who had received at least 6 months' chemotherapy were evaluated. EPO significantly increased Hb levels, lengthened the time to first transfusion and decreased the proportion of transfused patients. Of transfusion dependent patients at baseline, more EPO treated patients became transfusion independent. Musto et al.[165] also reported that 35.1% of patients with advanced, transfusion-dependent and chemoresistant disease required no transfusions after 2 months of EPO therapy. Silvestris et al.[166] recently observed that patients receiving chemotherapy combined with IFNα and EPO increased serum IgM, suggesting that IFNα plus EPO may be effective in restoring normal B cell function as observed in an *in vitro* study. Administration of EPO at 10 000U 3 times a week is highly effective for most patients, but some patients may require higher doses to increase their haemoglobin levels.[167]

3.3 Renal Insufficiency

Renal failure occurs in 15 to 30% of patients at presentation, but will develop in half of patients during the course of their disease. It has multiple possible causes, such as cast nephropathy, hypercalcaemia, amyloidosis or light chain deposition. Cast nephropathy (myeloma kidney) is due to precipitation of Bence Jones proteins within the distal tubule combined with Tamm-Horsfall glycoprotein, leading to intraluminal obstruction and renal failure. The type and amount of Bence Jones proteins and tubule fluid flow rate are the primary factors influencing this cast formation, while dehydration, radiocontrast agents and diuretic-induced hypercalciuria facilitate progression of the cast nephropathy. Hydration, control of hypercalcaemia and effective chemotherapy will reverse renal dysfunction within several months in more than half of patients. Chemotherapy regimens with a rapid response such as VAD are preferable. Rapid progressive renal failure in untreated patients may require multi-modal treatment such as plasmapheresis, short term haemodialysis and aggressive chemotherapy to prevent ESRD. Patients with acute or subacute renal failure are more likely to benefit from plasmapheresis than those with advanced myeloma. ESRD in younger patients due to myeloma kidney or amyloid light-chain (AL) amyloidosis limited to the kidneys should be considered for renal transplantation. Prolonged survival has been observed in many cases.[23,167,168]

3.4 Amyloidosis

About 15% of patients with myeloma also have the additional complication of AL amyloidosis, in which Ig light chains are deposited as insoluble fibrils in vital organs such as the kidney, heart, liver, gastrointestinal tract and autonomic and peripheral nerves. Patients with AL amyloidosis, with or without myeloma, typically live only 12 to 24 months from diagnosis.[23,169] Chemotherapy is the treatment of choice for amyloidosis patients with MM. Standard chemotherapy (MP) has been shown to prolong survival in several clinical trials, while the addition of colchicine to MP did not improve clinical outcome.[99,170]

Recently, Comenzo et al.[169] treated 5 patients with high dose melphalan and growth factor-mobilised autologous PBSC support. After a median follow-up of 13 months, 3 patients remain in CR. All patients experienced improved performance status and clinical remission of organ-related dysfunction. This pilot study suggests that dose-intensive chemotherapy can be used safely in AL amyloidosis and may result in significant clinical improvement in some patients.

A preliminary study[171] has shown that a new anthracycline, iododoxorubicin (4'-iodo-4'-deoxydoxorubicin; I-DOX), produced substantial clinical improvement in 5 of 8 patients with AL amyloidosis. Three patients presented objective evidence of amyloid resorption. The mechanism of action is independent of its cytotoxicity and appears caused by binding to amyloid fibrils. I-DOX caused transient granulocytopenia and minimal extra-haematological adverse effects. This study suggests that I-DOX may have an important impact in the treatment of amyloidosis.

4. New Developments in the Treatment of Multiple Myeloma

4.1 Chemosensitisers

Drug resistance remains a significant obstacle to improving therapeutic outcome in MM. Many studies have indicated that, depending on the dose and cytotoxic agent administered, different mechanisms of drug resistance may be involved. It was noted that P-glycoprotein (P-gp) is associated with resistance to doxorubicin and vincristine. Both are commonly used in the VAD regimen. Lung-resistance protein (LRP) expression is associated with melphalan resistance, and increased levels of gluthione-S-transferase (GST) are related to alkylating agent resistance, while overexpression of IL-6 and the Bcl-2/Bax family protein inhibit drug-induced apoptosis.[9,172,173]

It was recently observed that LRP-mediated melphalan resistance can be circumvented by dose

intensification,[45] and that P-gp-related multiple drug resistance (MDR) may be reversed by P-gp modulators. Thus, several noncytotoxic P-gp modulators, including verapamil, dexniguldipine, cyclosporin (cylosporine A), dexverapamil, quinine, valspodar and elacridar (GF120918), have been employed in clinical trials in an attempt to overcome drug resistance.[80,173-176] Some of them, such as verapamil and dexniguldipine, that originally exhibited promising *in vitro* activity, caused serious dose-limiting toxicity and did not show clinical benefit in MM.[173,174] The combination of cyclosporin with VAD in refractory MM specifically eliminated P-gp+ myeloma cells.[80,173,176] This regimen increased the complete remission rate and duration of response, but did not influence the response rate, progression-free survival and overall survival.

A second generation P-gp modulator, valspodar, a cyclosporin D analogue, which is more potent and not immunosuppressive, has demonstrated the potential for reversing drug resistance in MM patients.[175] 22 patients with VAD-refractory or melphalan-refractory disease were treated with 3 cycles of VAD plus an escalating dose of valspodar (2.5 to 15 mg/kg). The main dose-limiting toxicity was myelosuppression and transient cerebral dysfunction.[177] A partial response was observed in 10 of 22 patients, including 4 of 8 assessable melphalan-refractory patients and 6 of 12 assessable VAD-refractory patients. A 25% dose reduction in VAD was necessary in 10 patients because of a more than 50% increase in serum levels of doxorubicin.[173,176] The increased plasma half-life and larger area under the curve (AUC) of doxorubicin in patients treated with valspodar has also been noted in other studies.[177] As a result of the altered pharmacokinetics of chemotherapeutic agents administered concurrently with valspodar, an approximately 2- to 3-fold dose reduction in these chemotherapeutic agents is often required, without compromise of the antitumour efficacy of chemotherapy.[173,177,178] More potent P-gp inhibitors, such as GF120918, an acridine derivative, have been developed and are entering clinical trials.[177,179] In addition, anti-P-gp monoclonal antibodies (MAbs) may also be useful for eliminating P-gp+ tumour cells and sensitising tumour cells to cyclosporin and chemotherapy.[8]

4.2 Immunotherapy

Immunotherapy offers another attractive alternative for MM, particularly for minimal residual disease after chemotherapy. This approach includes the utilisation of anti-tumour MAbs, toxins coupled to antibodies or IL-6 (immunotoxins) and growth factor inhibitors to destroy tumour cells directly or to interfere with the signalling of growth factors. Idiotypic vaccines, cytokines and cellular therapy have been designed to boost host antitumour immunity.[8,87,180-182] Several antibodies or immunotoxins have been evaluated in small clinical trials for systemic treatment or *ex vivo* purging of autologous bone marrow. Thus, anti-IL-6 MAbs have demonstrated some biological effects, such as transient tumour suppression, resolution of fever and hypercalcaemia, and complete inhibition of c-reactive protein in advanced patients, but improved outcome or achieved remission has not been observed.[33,183]

A preliminary study showed that administration of humanised anti-IL-6 receptor MAb rhPM-1 to patients with advanced MM ameliorated tumour-associated toxicity.[184] A combination of high dose chemotherapy and anti-B-cell/plasma cell MAbs-treated autologous BMT have achieved high response rates and prolonged progression-free survival in some patients, but relapses and slow engraftment post-BMT in heavily pretreated patients suggest that such treatment strategies should be used earlier in the disease course.[87] Low dose IL-2 was administered subcutaneously in 18 patients with advanced, progressive disease who failed conventional chemotherapy. Two of the 17 evaluable patients had objective tumour mass reduction and 4 others had long-lasting stabilisation of the disease.[185]

Monoclonal Igs produced by myeloma cells are a unique tumour-specific antigen for idiotype (Id) vaccination, and have been used to immunise a

healthy sibling donor before marrow transplantation. An idiotype-specific T-cell response was generated in the donor and successfully transferred to the recipient.[186] Three of 5 patients vaccinated with autologous M-component precipitated in aluminium showed an induction of specific cellular and humoral immunity.[180]

Dendritic cells are potent antigen presenting cells and are being actively investigated at present for their ability to elicit an antitumour immune responses.[187-189] A preliminary study demonstrated that an advanced MM patient who received blood dendritic cells pulsed with Id produced a potentially beneficial anti-myeloma Id-specific immune response that persisted after high dose chemotherapy.[188] In addition, anti-CD38 immunotoxin, humanised anti-CD38 MAb, anti-CD54, HM1.24, anti-IL-6R antibodies, IL-6 antagonists, IL-6 toxin fusion proteins and soluble CD16 have also shown potent antitumour activity *in vitro* or in human myeloma animal models.[87,190-199] Moreover, gene transfer of IL-2, interleukin-12 (IL-12) and the costimulatory molecules B7-1 and B7-2 into human myeloma cells also hold promise for inducing antitumour responses.[200,201]

Depletion of donor T cells, by using anti-T cell antibodies and complement prior to allogeneic or syngeneic BMT to reduce the incidence and severity of GVHD, has been reported in a small clinical study.[87] Only 10% (2 of 21) patients developed severe GVHD, and there were no deaths attributable to GVHD, suggesting that this approach warrants further investigation.

5. Conclusion

Despite substantial progress in the elucidation of the molecular pathogenesis and management of MM, the disease still remains incurable. More effective and better tolerated therapy regimens are needed. Although optimal regimens for the initial therapy of MM have not yet been defined, conventional chemotherapy has been demonstrated to increase event-free survival and prolong overall survival. Combination chemotherapy has resulted in higher response rates, longer response duration and higher 5-year survival than standard chemotherapy for good-risk patients. High dose chemotherapy with autologous PBSC and BMT significantly increases complete remission rates and prolongs survival, and should be considered whenever possible for eligible patients. Long-lasting remission (almost 10 years) was observed in about 10% of cases after autologous PBSC or BMT in advanced and refractory MM, suggesting that cure may be achievable.[25,113] Tandem transplantation or allogeneic transplantation may be beneficial for selected patients.

Continued research to identify a reliable and accurate method for predicting prognosis in individual patients is imperative. Earlier initiation of treatment and a more aggressive and intensive approach may be required for high risk patients in order to improve their clinical outcome. Clinical application of the potent P-gp modulators may reverse some chemoresistant disease, and incorporation of P-gp modulators into front-line therapy at earlier stages of disease may prevent or delay the emergence of drug resistance.

The use of IFN is still controversial. Early recognition and treatment of complications of the disease, such as anaemia or bone lesions, are extremely important, and result in significant improvement in disease outcome and quality of life.[7,137] Preliminary results of immunotherapy, such as idiotypic vaccination and antibody-purged BMT, are encouraging. Continuous application of our expanding knowledge of immunology, molecular biology and myeloma biology to the development of novel biological therapies may have significant therapeutic impact in the near future. A combination of several distinct strategies may allow further improvement in disease outcome.

Acknowledgements

The authors thank Dr Frank Forte and Dr Marcel Odaimi for their critical comments and Dr Thomas McGinn for his support.

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