Multiple Myeloma – Inching Towards A Cure

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ABSTRACT

Multiple Myeloma is a disease of plasma cells that has fatal consequences. Use of high-dose chemotherapy with autografting has substantially increased the frequency of complete remissions in the disease and has lengthened progression-free survival and overall survival compared with conventional chemotherapy. However, patients invariably relapse and salvage chemotherapy is not very effective. The technique of allografting is though to be the only potentially curative treatment of myeloma because of the significant graft-versus-myeloma effect, but is associated with a high risk of transplant-related mortality. Clinical trials that use non-myeloablative conditioning have shown encouraging results, but a longer follow-up is needed to determine the exact therapeutic role of this approach. A better understanding of the biology of myeloma has culminated in the development of rational drugs that target specific intercellular pathways and the crosstalk that occurs between the myeloma cell and the microenvironment. Clinical trials of these new drugs have shown promising results and indicate that, in addition to the myeloma cells, the targets of therapy should also be the microenvironment that sustains these cells. The activity of these agents, either singly or in combination, with conventional as well as high-dose chemotherapy, overcomes resistance to chemotherapy in many patients who have undergone multiple cycles of treatment. This advantage provides the rational for their further combinations to take advantage of this synergism. Major challenges lie ahead to investigate and determine the most active and ideal combinations, as induction or consolidation treatments with the ultimate goal of converting the disease into a chronic phase, extending survival, and improving quality of life in most and also curing a few patients.

INTRODUCTION

Multiple myeloma is a plasma cell malignancy characterized by uncontrolled proliferation of monoclonal malignant plasma cells in the bone marrow. Clinically, the disease encompasses a wide spectrum of syndromes ranging from asymptomatic indolent or smouldering myeloma to florid disease with extensive bone marrow and bone involvement with or without renal failure. Laboratory hallmarks of the disease include the presence of a monoclonal protein band in the serum and/or the urine detected by electrophoresis and bone marrow infiltration by malignant plasma cells.

As of today, multiple myeloma is not considered a curable cancer, but survival of more than a decade is the rule after appropriate treatment. In the past decade there have been major advances in the understanding of the biology of myeloma, the interactions between the myeloma cell and the stomal cells (Fig. 1), the various prognostic factors and the immunology of the disease. As a result, a number of new treatment strategies and new drugs have become available for the treatment of this disease.

In the present review, after a brief introduction and over-view of the existing knowledge of the disease, the emphasis will be on newer concepts and emerging paradigms in the therapy of this disease, especially the newer targeted molecules now being tested for this cancer.

TYPES OF MYELOMA

A patient's myeloma is often referred to by the type of immunoglobulin or light chain (kappa or lambda type) produced by the malignant plasma cell. The frequency of the various immunoglobulin types of myeloma parallels the normal serum concentrations of the immunoglobulins. The most common myeloma types are IgG and IgA. IgG myeloma accounts for about 60% to 70% of all cases of myeloma and IgA accounts for about 20% of cases. Few cases of IgD and IgE myeloma have been reported.

Although a high level of M protein in the blood is a hallmark of myeloma disease, about 15% to 20% of patients with myeloma produce incomplete immunoglobulins, containing only the light chain portion of the immunoglobulin (Bence Jones proteins) - light chain myeloma. In these patients, M protein is found primarily in the urine, rather than in the blood. Nonsecretory myeloma affects about 1% of myeloma patients.

Classification of Myeloma

Patients may be classified into 4 categories depending on treatment requirement. Patients in some categories do not

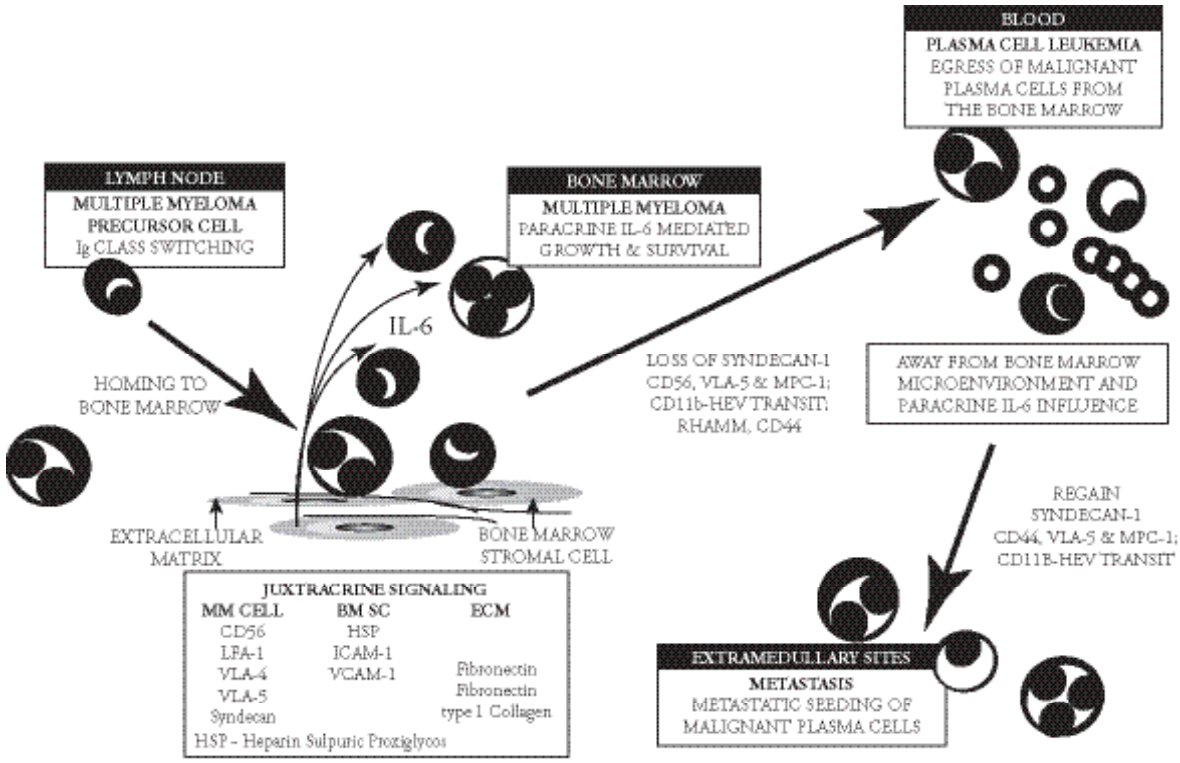

Fig. 1: Myeloma cell - stromal cell interactions in myeloma: Role of adhesion molecules in the pathogenesis.

have to receive treatment immediately. In some low-risk cases, postponing therapy may help avoid unnecessary side effects and the risk of complications associated with chemotherapy and delay development of resistance to chemotherapy.

Monoclonal Gammopathy of Undetermined Significance (MGUS)

Monoclonal gammopathy of undermined significance (MGUS) is a condition where a monoclonal protein is present in the serum or the urine. However, these patients are asymptomatic and other criteria for myeloma diagnosis are absent, and no cause for the increased protein can be identified. MGUS occurs in about 1% of the general population and in about 3% of normal individuals over 70 years of age.

MGUS is considered to be a benign disorder, but about 15-25% of patients with MGUS will progress to a malignant plasma cell disorder. Currently, no laboratory tests are available that can predict which patients with MGUS will progress to multiple myeloma. For this reason, patients with MGUS are observed and are only treated if the disease progression to a plasma cell malignancy is documented.

Smoldering Multiple Myeloma (SMM)

Patients with smoldering myeloma have a monoclonal protein and increased numbers of plasma cells in the bone marrow. However, they are asymptomatic and have no anemia, bone disease, renal failure, or recurrent infections. In these patients the myeloma is considered to be static and may not progress for months or years. Current recommendation for patients with smoldering myeloma is observation with treatment reserved for when there is disease progression. About 5% of myeloma patients are classified with smoldering myeloma at diagnosis.

Indolent Multiple Myeloma (IMM)

Patients with indolent myeloma are also asymptomatic. They have a monoclonal protein and increased numbers of plasma cells in the bone marrow, and may also have mild anemia or a few bone lesions. Patients with indolent myeloma are monitored every 3 months and are treated if there is evidence of disease progression.

Symptomatic Multiple Myeloma (MM)

Patients who present with symptoms typically have a monoclonal protein and increased numbers of plasma cells in the bone marrow. Anemia, renal failure, hypercalcemia, or bone lesions are usually present in various severity and combinations. Patients with symptomatic myeloma require immediate treatment. The characteristics and management strategies for each of these classification categories are summarized in the Table 1.

STAGING OF MYELOMA

Proper staging of the severity of myeloma disease helps determine a treatment plan. The Durie-Salmon staging system has been in use since 1975 (Table - 2). In this system, the clinical stage of disease (stage I, II, or III) is based on several measurements, including levels of M protein, the number of bone lesions, hemoglobin values, and serum calcium levels. Stages are further divided according to renal function as determined by serum creatinine levels (classified as A or B).

PROGNOSTIC FACTORS

Several clinical and laboratory factors have been identified which provide important prognostic information (Table 3).[1-3]

Table 1: Classification of Multiple Myeloma

Classification	Characteristics	Management
Monoclonal gammopathy of undetermined significance (MGUS)	• Serum M protein <3 g/dL • Bone marrow plasma cells <10% • Absence of anemia, renal failure, hypercalcemia, and lytic bone lesions	Observation, with treatment beginning at disease progression
Smoldering multiple myeloma (SMM)	• Serum M protein <3 g/dL *and/or* • Bone marrow plasma cells <10% • Absence of anemia, renal failure, hypercalcemia, and lytic bone lesions	Observation, with treatment beginning at disease progression
Indolent multiple myeloma (IMM)	• Presence of serum/urine M protein • Bone marrow plasmacytosis • Mild anemia or few small lytic bone lesions • Absence of symptoms	Monitoring every 3 months, with treatment beginning at disease progression
Symptomatic multiple myeloma (SMM)	• Presence of serum/urine M protein • Bone marrow plasmacytosis • Anemia, renal failure, hypercalcemia, or lytic bone lesions • Patients with primary systematic amyloidosis and bone marrow plasma cells ≥30% are considered to have both MM and amyloidosis	Immediate treatment

Table 2: Durie-Salmon Staging System of Multiple Myeloma

Stage	Criteria	Measured myeloma cell mass
I	All of the following: • Hemoglobin value >10 g/dL • Serum calcium value normal or ≤12 mg/dL • Absence of anemia, renal failure, hypercalcemia, and lytic bone lesions • Low M-component production rate • IgG value <5 g/dL; IgA value <3 g/dL • Bence Jones protein <4g/24 h	<0.6 cells x $10^{12}/m^2$ (low cell mass)
II	Fitting neither stage I nor stage III	0.6-1.2 cells x $10^{12}/m^2$ (intermediate cell mass)

III	One or more of the following:
	• Hemoglobin value <8.5 g/dL
	• Serum calcium value >12 mg/dL
	• Advanced lytic bone lesions (scale 3)
	• High M-component production rate
	  • IgG value >7 g/dL; IgA value >5 g/dL
	  • Bence Jones protein >12 g/24 h
		>1.2 cells x $10^{12}/m^2$ (high cell mass)

Subclassification (either A or B)
A: Relatively normal renal function (serum creatinine value <2.0mg/dL)
B: Abnormal renal function (serum creatinine value ≥2.0 mg/dL)

TREATMENT OPTIONS

In the past one decade, there has been tremendous progress in the field of myeloma research and scientific advances now offer an unprecedented opportunity to treat myeloma patients. Because of these advances there is now a much better understanding of the genetic defects producing myeloma, the basic biology of the myeloma cell, its interaction with other myeloma cells and the stromal cells and the biology and understanding of myeloma bone disease. These basic advances have translated into the development of many unique treatment molecules and lead to the widening of the therapeutic options and armamentarium against all stages of the disease.

Treatment of myeloma can be a complex process because many variables must be taken into account, such as stage of disease, age, and whether a patient has received previous therapy. Moreover, there is no single test result that can lead to a diagnosis of myeloma, determine the prognosis and define ideal treatment; many factors must be considered.[4,5]

With the many promising therapies in clinical trials, there is a realistic hope to strive towards the goal of a cure for myeloma in the near future.

Goals of Treatment

Treatment regimens may be designed to meet one or more different therapeutic goals. Therapeutic goals of treatment include:

1. Controlling disease activity to prevent damage to various organs in the body
2. extending disease-free survival and overall survival
3. providing lasting relief of pain and other disease symptoms
4. preservation of normal performance and quality of life for as long as possible

Table 3: Prognostic Factors in Myeloma

Test	Description	Values indicating favourable prognosis
Beta 2-microglobulin	A protein normally found on the surface of cells; serum levels reflect the extent of disease	<3 þg/mL
Plasma cell labeling index (PCLI)	The relative percentage of plasma cells actively growing; a low PCLI may indicate longer survival	<1%
C-reactive protein (CRP)	Increased levels of this protein produced by the liver may indicate poorer prognosis	<6 þg/mL
Lactate dehydrogenase (LDH)	Measures tumor-cell burden	Age ≤60 y: 100-190 U/L Age >60 y: 110-210 U/L
Plasmablastic morphology	The general appearance of plasma cells; increased numbers of immature plasma cells (plasmablasts) indicates poor prognosis	Absence of plasmablastic morphology
Chromosome analysis (cytogenetic testing)	Assesses the number and normalcy of chromosomes; for example, fluorescence *in situ* hybridization (FISH) is a test that detects abnormalities of specific chromosomes, deletion of chromosome 13 confers a poor prognosis	Normal chromosome 13
Bone marrow microvessel density (MVD)	Measures the growth of new blood vessels (angiogenesis) in the bone marrow; increased MVD indicates poorer prognosis	<6 vessels/field at 400x magnification

Potential Outcomes of Treatment

There are several potential outcomes of treatment in myeloma, which are summarized in the Table 4.

Although cures have not been documented in patients with myeloma, molecular complete responses have been achieved with some of the new therapies in clinical trials. Relapses can occur after molecular complete response, usually after a longer period of relapse-free survival. Evolving therapies may offer patients a greater chance of achieving a molecular and consequentially, permanent cure of the disease.

Disease Status

The treatment options available to a patient take into account their disease status, that is, whether they have already received therapy and if so, what was the outcome.

Table 4 : Potential Treatment Outcomes in Myeloma

Treatment Outcome	Definition
Cure	No evidence of disease (this has not yet been achieved in myeloma)
Molecular complete response	No evidence of myeloma cells in the bone marrow using sensitive molecular techniques. These techniques continue to evolve and become more sensitive, so this definition is constantly changing and becoming more stringent.
Complete response (CR)	No detectable M protein in the serum and urine (using immunofixation) and Normal percentage of plasma cells in the bone marrow or Absence of myeloma cells by staining techniques
Very good partial response (or near complete response)	Greater than 90% decrease in M protein
Partial response (PR)	Greater than 50% decrease in M protein
Minimal response (or minor response)	Less than 50% decrease in M protein (some myeloma groups consider minimal response to be part of the definition of stable disease)
Stable disease (SD)/ plateau phase	Stable disease parameters (including number and extent of lesions) with some decrease in M protein
Progressive disease	Greater than 25% increase in M protein, new bony lesions, or a new plasmacytoma

Patients who have received therapy may fall into several categories:

- Responsive disease - myeloma that is responding to therapy. There has been a decrease in M protein of at least 50%.
- Plateau refers to a response to therapy that has reached a certain point and has not continued any further
- Stable disease - myeloma that has either:
- Stabilized during active therapy, whereby it has not responded to treatment (i.e., the decrease in M protein has not reached 50%) but it has not progressed, or
- Stabilized after therapy has been stopped. In this case, the myeloma has stabilized in response to therapy. The number and extent of bony lesions is stable and there may be a slight decrease in M protein
- Progressive disease - myeloma disease that continues to progress despite therapy
- Relapsed disease - myeloma disease that initially responded to therapy but has then begun to progress again
- Refractory disease - myeloma that has not responded to initial therapy, as well as relapsed myeloma that does not respond to subsequent treatment. In this last instance, the myeloma may also be referred to as relapsed and refractory disease.

Treatment Options

The possible treatment options listed in the Tables below are grouped according to previous history of therapy:

Table 5 : Treatment Options for Newly Diagnosed Patients of Multiple Myeloma

Myeloma Category	Treatment Options
Monoclonal gammopathy of undetermined significance (MGUS)	• Observation until disease progresses, then treatment as indicated for active disease
Smoldering myeloma (SMM) Stage I disease Active disease (Stage II or III)	• Standard chemotherapy and supportive care as required Note: Patients who may be candidates for autologous stem cell transplant should preferably not be given alkylating agents (e.g., melphalan) because these agents can lead to poor harvest of stem cells.

Table 6: Treatment Options for Patients Who Have Received One Form of Primary Treatment

Disease Status	Treatment Options
Responsive	• Continuation of current therapy until plateau is reached • Autologous stem cell transplant • Allogeneic stem cell transplant if a HLA matched-donor is available
Stable	• Continuation of current therapy until plateau is reached • Autologous stem cell transplant • Allogeneic stem cell transplant
Plateau	• Observation, with supportive care as required • Maintenance therapy with steroids, interferon or thalidomide • Autologous stem cell transplant
Refractory disease	• Salvage chemotherapy, thalidomide, or thalidomide plus dexamethasone
Relapsed disease	• Repeat of primary therapy if relapse occurs after 6 months of discontinuing therapy • Salvage chemotherapy, thalidomide, or thalidomide plus dexamethasone, depending on the speed of disease progression • Allogeneic stem cell transplant

- Newly diagnosed patients who have not received therapy (Table 5)
- Patients who have received one therapy (Table 6)
- Patients who have received more than one therapy (Table 7)

Chemotherapy

Chemotherapy may consist of a single medication or a combination of drugs, which are administered intravenously or orally. Most patients with active, symptomatic myeloma (stage II or III) are initially treated with some form of chemotherapy. There are several forms of chemotherapy that patients with myeloma receive. These include

Table 7: Treatment Options for Patients Who Have Received More Than One Therapy for Myleoma.

Disease Status	Treatment Options
Responsive	• Observation, with supportive care as required • Maintenance therapy with steroids or interferon • Autologous stem cell transplant • Continuation of current therapy until plateau • Stem cell transplant (autologous or allogeneic)
Stable	• Observation, with supportive care as required • Maintenance therapy with steroids or interferon
Plateau	• Observation, with supportive care as required • Maintenance therapy with steroids or interferon • Stem cell transplant (autologous or allogeneic)
Refractory disease	• Salvage chemotherapy, thalidomide, or thalidomide plus dexamethasone • Salvage therapy • Allogeneic stem cell transplant
Relapsed disease	• Salvage chemotherapy, thalidomide, or thalidomide plus dexamethasone • Salvage therapy • Allogeneic stem cell transplant

- Conventional chemotherapy
- High-dose chemotherapy with stem cell transplantation
- Salvage therapy

Treatment options for patients with symptomatic myeloma range from pulse dexamethasone with or without thalidomide, conventional chemotherapy to high-dose chemotherapy and peripheral stem cell or allogeneic bone marrow transplantation. Treatment choice is determined largely by the age and general health of the patient and should be finely attuned to the preferences of patients and their families.

Conventional chemotherapy using alkylators prolongs the survival of patients with symptomatic myeloma to a median of 40 to 46 months for patients with stage I disease, 35 to 40 months for patients with stage II disease, and 24 to 30 months for patients with stage III disease. At this time, however, most patients begin with nonalkylator therapy to avoid exposing the tumor to these drugs prior to autologous or allogeneic stem cell transplantation therapy, which involves high doses of these drugs. The two most common induction regimens are high-dose pulse dexamethasone with or without thalidomide[6-8] or VAD (vincristine + doxorubicin + dexamethasone).[9,10]

The following are the current active strategies for treatment of multiple myeloma:

1. High-dose corticosteroids.
2. Antiangiogenic agents such as thalidomide.
3. Conventional chemotherapy.
4. Autologous or allogeneic peripheral stem cell transplantation.
5. Proteasome inhibitors such as bortezomib.
6. Investigational agents: IMIDS (Revlimid, Actimid), antisense oligonucleotides (Genasense), arsenic trioxide.

Table 8 : Commonly Used Conventional Chemotherapy Regimens for Multiple Myeloma

Abbreviation	Components	Suitable for use as induction therapy?
MP	Melphalan, prednisone	Yes*
C-weekly	Cyclophosphamide, prednisone	Yes
VBMCP	Vincristine, BCNU (carmustine), melphalan, cyclophosphamide, prednisone	No
ABCM	Doxorubicin, BCNU, cyclophosphamide, melphalan	No
VMCP/VBAP	Vincristine, melphalan, cyclophosphamide, prednisone/ vincristine, BCNU, doxorubicin, prednisone	No
VAD	Vincristine, doxorubicin, dexamethasone	Yes
D	Dexamethasone	Yes
TD	Thalidomide, dexamethasone	Yes
DVd	Liposomal doxorubicin, vincristine, reduced-dose dexamethasone	Yes
DVd-T	Liposomal doxorubicin, vincristine, reduced-dose dexamethasone, thalidomide	Under investigation
CT	Cyclophosphamide, thalidomide	Under investigation
DCEP	Dexamethasone, cyclophosphamide, etoposide, cisplatin	Under investigation
DT-PACE	Dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide	Under investigation

* Many clinicians avoid using melphalan as induction therapy because it may reduce the number of cells that can be harvested in preparation for a stem cell transplant.

Typical regimens used in conventional chemotherapy of myeloma – first line (Table 8) and salvage (Table 9) are as follows:

1. VAD[9-11]
2. Oral thalidomide alone or in combination with high-dose dexamethasone[7,8,12-15]
3. High-dose dexamethasone[6]
4. Cyclophosphamide plus prednisone[16]
5. Autologous or allogeneic stem cell transplantation[17-23]
6. Bortezomib (proteasome inhibitor)[24]
7. Melphalan and prednisone[25-27]
8. VBMCP (the M2 protocol: vincristine + carmustine + melphalan + cyclophosphamide + prednisone)[26,28]
9. VMCP/VBAP (vincristine + melphalan + cyclophosphamide + prednisone alternating with vincristine + carmustine + doxorubicin + prednisone)[26,29]

Table 9 : Commonly Used Salvage (second-line) Chemotherapy Regimens for Multiple Myeloma

Abbreviation	Components
CVAD or Hyper-CVAD	Cyclophosphamide, VAD (vincristine, doxorubicin, dexamethasone)
EDAP	Etoposide, dexamethasone, ara-C, cisplatin
--	High-dose or low-dose cyclophosphamide
--	Thalidomide
--	Bortezomib (bortezomib)
MTD*	Melphalan, thalidomide, dexamethasone
TD*	Thalidomide, dexamethasone
DVd-T*	Liposomal doxorubicin, vincristine, reduced-dose dexamethasone, thalidomide
ThaCyDex or Hyper CDT*	Thalidomide, cyclophosphamide, dexamethasone

*Under investigation

Table 10: Dosing and Administration Recommendations for Optimizing Thalidomide Therapy

Thalidomide Dose

- Start at 100-200 mg/day.*
- In patients with aggressive disease, including those with high tumor burden and high-risk factors, an initial dose of ≥200 mg/day as part of combination therapy (e.g. thalidomide plus dexamethasone) is suggested.†
- Lower starting doses may be employed in elderly patients and those with other conditions
- Increase dose by 50-100 mg/day every 1-2 weeks
- Target therapeutic dose: 200 mg/day by 2 weeks, with further dose escalation as tolerated at physician discretion

Managing Toxicities

- Administer thalidomide earlier in the evening (7-10 PM) to reduce sedation.
- Dose reduction may be helpful for symptomatic neuropathy. In more severe cases, temporarily stopping the drug may improve symptoms and allow thalidomide to be reinitiated at a lower dose.

Assessing Response and Continuing Therapy

- Assess response at 1 month.
- Continue therapy indefinitely as long as:
  - Response (complete, partial, or minor) or stable disease is maintained
  - Thalidomide-related toxicity is manageable
  - There are no uncontrolled disease-related symptoms
- In cases of disease progression:
  - Continue thalidomide in combination with dexamethasone and/ or other treatments
  - Consider alternative therapy

*Lower thalidomide doses (i.e., 50 mg/day) are commonly used in clinical practice.

†Some clinicians recommend a maximum dose of 200 mg/day when thalidomide is used as part of combination therapy and 400 mg/day when used alone in order to minimize side effects.

High-dose corticosteroids

Dexamethasone is given at a dose of 40 mg orally for four consecutive days in the same schedule as given with the VAD

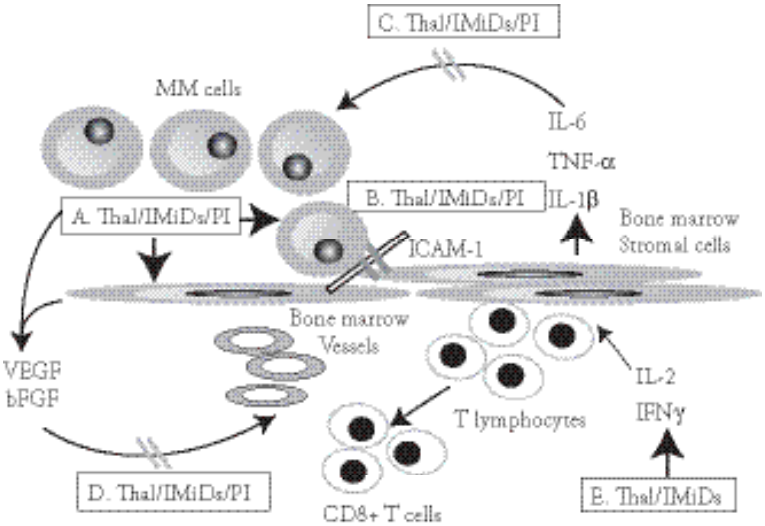

Fig. 2 : Potential mechanisms of action of Thalidomide and IMIDS in myeloma

Table 11 : Ongoing Phase II and III Thalidomide Combination Trials

Relapsed and Refractory Myeloma – Thalidomide in combination with

- Sargramostim (granulocyte-colony stimulating factor)
- Cyclophosphamide
- Arsenic trioxide
- Liposomal doxorubicin, vincristine, and dexamethasone
- An autologous dendritic cell vaccine
- High-dose melphalan followed by stem cell transplant
- Bortezomib
- Bortezomib plus liposomal doxorubicin
- Genasense (oblimersen)

Newly diagnosed patients – Thalidomide in combination with

- Vincristine, adriamycin, and dexamethasone
- Dexamethasone and clarithromycin
- Zoledronic acid and dexamethasone
- Liposomal doxorubicin, vincristine, and dexamethasone (DVD-T regimen)
- An intensive treatment regimen involving two stem cell transplants (Total Therapy II)
- An intensive treatment regimen involving two stem cell transplants and bortezomib therapy (Total Therapy III)

Smoldering/Indolent Myeloma – Thalidomide in combination with

- Pamidronate
- Zoledronic acid

As Maintenance – Thalidomide in combination with

- Prednisone (following stem cell transplant)

regimen.[6] Response rates of 60% to 70% in previously untreated patients appear just as high as those in patients treated with VAD in this phase II trial.[6] The advantages of this regimen include the following:

- Ease of administration.
- Lack of significant hematologic toxic effects.
- Applicability for elderly patients and for those with poor performance status.
- Avoidance of alkylating agent chemotherapy which might be better applied at a later time.

There are no randomized studies to support the widespread use of high-dose dexamethasone with or without thalidomide.

Thalidomide (antiangiogenesis agent)

Thalidomide in the treatment of myeloma is the major discovery of this century. Thalidomide is given orally on a daily basis (usually between 50 mg and 200 mg) (Table 10) and has shown activity in previously treated and untreated patients.[7,8,12-14] The mechanism of action is not known, but may involve antiangiogenesis, interference with adhesion molecules, and release of cytokines (Fig. 2). Thalidomide has been combined with dexamethasone for 70% to 80% response rates in previously untreated patients; the durability and long-term consequences of this primary therapy remain unknown.[8,15] No randomized studies support the widespread use of high-dose dexamethasone with thalidomide. Common side effects of thalidomide include sedation, constipation, peripheral neuropathy, and deep venous thrombosis (28% in one report when thalidomide was combined with dexamethasone).[25] Thalidomide has minimal hematologic toxic effects and is easy to administer. Immunomodulatory analogs of thalidomide are under evaluation in clinical trials. Combinations of thalidomide, dexamethasone, and conventional chemotherapy are also under evaluation.[30,31]

Thalidomide was initially demonstrated to be effective as a single agent and then in combination with dexamethasone and other chemotherapeutic agents in relapse and refractory myeloma in multiple studies producing a response in more than 50% of patients. More recently, thalidomide has been used in newly diagnosed, chemo-naïve patients and, in combination with dexamethasone, produces response rates in 70-80% patients, equal to response seen with the more toxic and cumbersome infusional VAD-like regimens.[15]

At the present time, there are at least 20 different trials ongoing using Thalidomide in combination with steroids or conventional chemotherapeutic agents in various stages and phase in patients with myeloma (Table 11).

Conventional-dose chemotherapy

The VAD regimen has shown activity in previously treated and in untreated patients, with response rates ranging from 60% to 80%.[9-11] No randomized studies support the widespread use of this regimen in untreated patients. This regimen avoids early exposure to alkylating agents, thereby minimizing any problems with stem cell collection (if needed) and future risks for myelodysplasia or secondary leukemia. Disadvantages include the logistics for a 96-hour infusion of doxorubicin and a low complete response rate. An alternative version of VAD substitutes pegylated liposomal doxorubicin for doxorubicin, eliminating the need for an infusion, with comparable response rates.[32,33]

Evidence is not strong that any alkylating agent is superior to any other. All standard doses and schedules produce equivalent results.[27] The two most common regimens historically have been oral MP (melphalan + prednisone) and oral cyclophosphamide plus prednisone.[16,25-27]

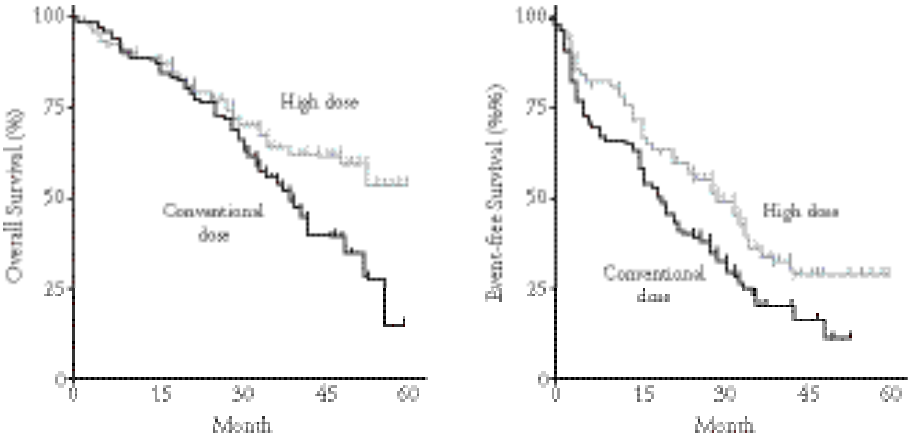

Fig. 3 : Overall and event-free survival - Superiority of high-dose versus conventional-dose chemotherapy (IFM-90 study):

Table 12 : Superiority of High-dose Versus Conventional-dose Chemotherapy (IFM-90 study)

Response category	Conventional-dose	High-dose
Response rate	57%	81%
Complete response rate	5%	22%
Median event-free survival (EFS)	18 Months	28 Months
EFS at 7 years	8%	15%
Median overall survival (OS)	44 Months	57 Months
OS at 7 years	25%	43%

Combinations of alkylating agents and prednisone, given simultaneously or alternately, have not proven to be superior to therapy with MP.[25,34-37] A meta-analysis of studies comparing melphalan plus prednisone with drug combinations concluded that both forms of treatment were equally effective.[27] Patients who relapsed after initial therapy with cyclophosphamide and prednisone had no difference in overall survival (median 17 months) when randomized to VBMCP or VAD.[38]

High-dose chemotherapy: autologous bone marrow or peripheral stem cell transplantation

The failure of conventional therapy to cure the disease has led investigators to test the effectiveness of much higher doses of drugs such as melphalan. The development of techniques for harvesting hemopoietic stem cells, from marrow aspirates or the peripheral blood of the patient, and infusing these cells to promote hemopoietic recovery made it possible for investigators to test very large doses of melphalan. From the experience with thousands of patients treated in this way, it is possible to draw a few conclusions:

1. The risk of early death due to treatment-related toxic effects has been reduced to less than 3% in highly selected populations. Patients can now be treated as outpatients.[23]
2. Extensive prior chemotherapy, especially with alkylating agents, compromises marrow hemopoiesis and may make the harvesting of adequate numbers of hemopoietic stem cells impossible.
3. Younger patients in good health tolerate high-dose therapy better than patients with poor performance status.[39,40]

The Intergroupe Français du Myélome[17] randomized 200 previously untreated myeloma patients younger than 65 years to treatment with conventional chemotherapy (alternating courses of VMCP/VBAP) versus high-dose therapy (140 mg melphalan/m^2 and total-body irradiation, 8 Gy delivered in four fractions over 4 days with no lung shielding, followed by autologous bone marrow rescue). Survival and disease-free survival were significantly improved in the high-dose arm (the estimated 5-year survival was 52% versus 12%; the estimated 5-year event-free survival was 28% versus 10%) (Table 12). Event-free survival is significantly better for the high-dose group (P=.01), but there is no sign of a slowing in the relapse rate, or a plateau, to suggest that any of these patients have been cured (Fig. 3).[17]

A prospective randomized trial of 401 previously untreated patients[41] younger than 65 years compared conventional-dose combination chemotherapy to high-dose therapy and autologous stem cell transplantation; the intensive therapy improved median survival from 42 months to 54 months (P=.04). In another prospective randomized trial, 193 patients with multiple myeloma received autologous peripheral stem cell transplantation after high-dose chemotherapy with or without CD34 selection.[18] Although CD34 selection reduced myeloma cell contamination in the stem cell collections, disease-free and overall survival were no different. Another prospective randomized trial of 261 previously untreated patients 65 years of age and under compared the VAD regimen followed by intensive consolidation with high-dose melphalan versus the same regimen followed by myeloablative therapy and autologous stem cell rescue; no difference in overall survival (50 versus 47 months, P=.41) could be seen with a median follow-up of 33 months.[42]

In summary, transplantation results in a significant but minor survival benefit of 12 to 15 months for patients younger than 60 to 65 years, with responsive or stable disease to induction chemotherapy, with good initial performance status, and with reasonable renal function (Fig. 4).[17,23,41] Any benefit of transplantation for older patients, for patients with renal insufficiency, and for patients with biologically aggressive disease remains unclear.[23]

Another approach to high-dose therapy has been the use of two sequential episodes of high-dose therapy with stem cell support (so-called tandem transplants).[20] In a trial of 399 previously untreated patients younger than 60 years, the patients were randomized to a single or double (tandem) autologous stem-cell transplantation.[43] With a median follow-up of more than 6 years, the double-transplant group had a superior event-free survival (20% versus 10% at 7 years, P=.03) and overall survival (42% versus 21% at 7 years, P=.01).[43] Patients with a reduction of paraprotein of more than 90% after the first transplant (the best

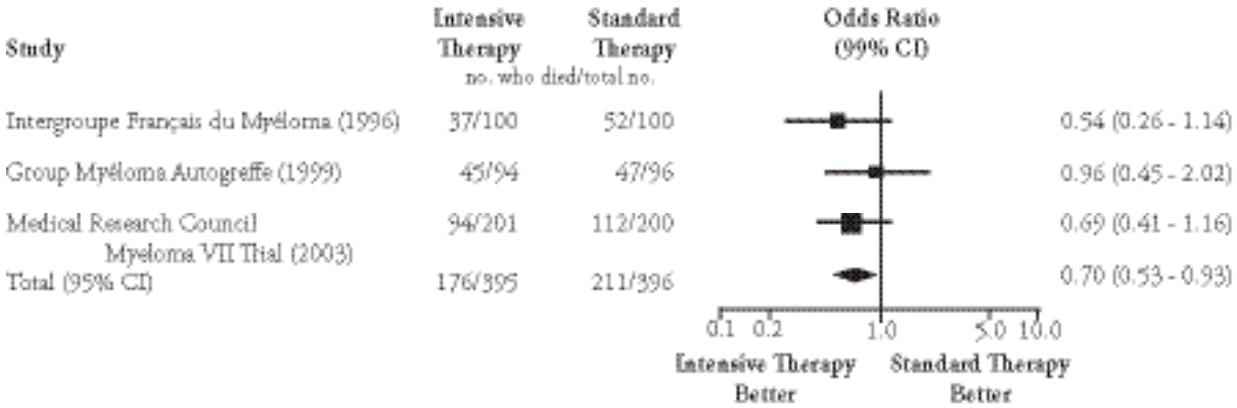

Fig. 4 : Forest plot showing odds ratio and 99 percent confidence intervals (CIs) in the three major studies comparing conventional chemotherapy versus high-dose chemotherapy in multiple myeloma:

responders) had the least incremental benefit from the second transplant (retrospective subgroup analysis).[43] Unpublished trials are ongoing to confirm these findings.

High-dose chemotherapy: allogeneic bone marrow or peripheral stem cell transplantation

In a registry of 162 patients who underwent allogeneic matched sibling-donor transplants, the actuarial overall survival rate was 28% at 7 years.[44] Favourable prognostic features included low tumor burden, responsive disease before transplant, and application of transplantation after first-line therapy. Many patients are not young enough or healthy enough to undergo these intensive approaches. A definite graft-versus-myeloma effect has been demonstrated, including regression of myeloma relapses following the infusion of donor lymphocytes.[21,45,46] Allogeneic marrow transplants have significant toxic effects (15%-40% morality), but the possibility of a potent, and possibly curative graft-versus-myeloma reaction makes this procedure attractive.[21] Further research is required to make allogeneic transplants less dangerous, and also, perhaps, to find methods for initiating an autoimmune response to the myeloma cells. At the Dana Faber Cancer Institute, there has been no difference in the overall survival and the progression-free survival at eight year between autologous versus allogeneic stem cell transplantation.

Mini (nonmyeloablative) Allogeneic Transplants

A new approach being investigated in myeloma is the use of a mini (nonmyeloablative) allogeneic transplant. Mini-transplants involve the use of moderately high-dose chemotherapy in combination with an allogeneic stem cell transplant. This dose of chemotherapy does not destroy the bone marrow completely, hence the name nonmyeloablative. For this reason, this type of transplant appears to be a safer and more tolerable alternative to conventional allogeneic transplants. Because they are allogeneic transplants, immune cells present in the allograft help kill myeloma cells (the graft-versus-myeloma effect).

Nonmyeloablative allogeneic stem cell transplant is under development. Such strategies aim to maintain efficacy (so called "graft-versus-tumor-effective") while reducing transplant-related mortality. Early reports indicate that significant graft-versus-host disease and transplant related mortality remain challenges with this approach.

Mini-transplants can be used alone or in combination with an autologous stem cell transplant. In this type of tandem transplant, patients first undergo an autologous stem cell transplant, which may provide substantial anti-tumor effects. This is followed by a mini-transplant from a matched donor two to four months later. This strategy is designed to provide a sequential anti-tumor effect from the two transplants and a potential graft-versus-myeloma effect from the allogeneic mini-transplant.

Mini-transplants are still being investigated in clinical trials. Preliminary results of a study of 41 patients receiving an autologous transplant followed by a mini-transplant. The study, which was conducted at the Fred Hutchinson Cancer Research Center, showed that the mini-transplant improved on the responses achieved with autologous transplants alone.[47,48]

Preliminary results of an ongoing Italian multicenter mini-transplant trial[47] involving patients up to 75 years of age with newly diagnosed myeloma were also reported. The data shows a high rate of sustained complete responses in patients receiving a mini-transplant following an autologous transplant. However, there are still high risks with these procedures and there are no long-term data regarding their efficacy and safety.

New Drugs in Myeloma

Bortezomib (proteasome inhibitor)

Bortezomib is the first of a new class of medicines called proteasome inhibitors and the first treatment in more than a decade to be approved for patients with multiple myeloma. It was approved in the US on May 13, 2003 and in the European Union on April 27, 2004 for the treatment of myeloma patients who have received at least two prior therapies and have demonstrated disease progression on the last therapy.

The proteasome is an enzyme complex that exists in all cells and plays an important role in degrading proteins involved in the cell cycle, angiogenesis, cell adhesion, cytokine production, apoptosis, and other important cellular processes. Many of the processes that rely on proteasome function can contribute to the growth and survival of cancer cells. Bortezomib is a potent but reversible inhibitor of the proteasome. By disrupting normal cellular processes, proteasome inhibition promotes apoptosis. Non-clinical data has demonstrated that cancer cells are more susceptible to the effects of proteasome inhibition than normal

Table 13 : Ongoing Bortezomib Clinical Trials in Myeloma

Phase II

- Phase II study of Bortezomib +/- dexamethasone in previously untreated myeloma patients
- Phase II study of Bortezomib, adriamycin and dexamethasone as primary therapy for myeloma
- UARK 2003-33, Total Therapy III: A Phase 2 Study Incorporating Bone Marrow Microenvironment (ME) - Co-Targeting Bortezomib into Tandem Melphalan-Based Autotransplants with DT PACE for Induction/Consolidation and Thalidomide + Dexamethasone for Maintenance

Phase I

- Studying the Pharmacokinetics and Pharmacodynamics of Bortezomib (bortezomib) in Patients with Relapsed Multiple Myeloma
- A Pilot Study of VDT (Bortezomib, liposomal doxorubicin and thalidomide) as Salvage Therapy for Patients with Relapsed or Refractory Multiple Myeloma (MM)
- Phase I study of Bortezomib and thalidomide in patients with refractory disease (University of Arkansas)

cells. Due to the reversibility of proteasome inhibition with Bortezomib, normal cells can recover from its effects, whereas cancer cells are more likely to undergo apoptosis.

Many of Bortezomib's anti-myeloma effects are thought to be due to its ability to block a key survival protein known as nuclear factor κB (NF-κB). NF-κB is found within the cell and acts as a transcription factor, turning on genes that cause production of proteins that stimulate cell growth.

When a cell receives an external signal, such as a growth factor, proteins such as NF-κB transfer the message to the nucleus of the cell, causing some type of response, such as cell growth. NF-κB also sends a message for cells to increase the expression of various molecules on their cell surface. In the case of myeloma, these surface molecules (adhesion molecules) allow myeloma cells to stick to cells in the bone marrow. This interaction stimulates the bone marrow cells to produce factors that promote the growth and survival of myeloma cells, such as interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF), which promotes angiogenesis.

Therefore, by blocking NF-κB, Bortezomib inhibits myeloma cell growth and induces myeloma cell death. It also inhibits the production of growth and survival factors by blocking the production of adhesion molecules on the myeloma cell surface and the interaction between myeloma and bone marrow cells. Angiogenesis is also inhibited as a result.

The recommended dose of Bortezomib is 1.3 mg/m^2/dose administered as an intravenous injection twice weekly for 2 weeks (days 1, 4, 8, and 11), followed by a 10-day rest period (days 12-21). Doses are typically given on Monday and Thursday or Tuesday and Friday. Duration of treatment is individualized, determined on patient's response and tolerability.

Final results of the multicenter Phase II SUMMIT trial of Bortezomib in patients with advanced relapsed and refractory myeloma were published in 2003. The data showed an impressive 35% overall response rate considering their condition and multiple lines of previous therapy.[24]

Results of a smaller, similarly designed Phase II dose-ranging trial (CREST, Study 024) of Bortezomib in 54 patients with earlier stage disease were also impressive. In this study, patients had either progressed on front-line therapy or relapsed at any time after front-line therapy. Their median number of prior therapies was 3 (range, 1 to 7). Overall responses of 30% and 50% were seen at the two doses tested (1.0 or 1.3 mg/m^2, respectively). Complete responses were seen in 4% of patients in both dose groups.[49]

Data are being evaluated from the recently ended Phase III APEX (Assessment of Proteasome Inhibition for Extending Remissions) trial in relapsed and refractory myeloma. The trial is comparing Bortezomib with high-dose dexamethasone, a recognized standard of care in this setting. Bortezomib (1.3 mg/m^2) is administered as an injection for eight 3-week cycles followed by three 5-week cycles. An independent data monitoring committee recommended an early end to the APEX trial. This was because the findings of a pre-specified interim analysis found a statistically significant improvement in time to disease progression—the primary endpoint of the trial—in patients receiving Bortezomib compared to patients receiving high-dose dexamethasone.

Bortezomib is being evaluated alone and in combination with a variety of agents in patients with refractory disease as well as in previously untreated myeloma patients. There are over 25 ongoing or planned clinical trials of Bortezomib in myeloma (Table 13).

Side effects include the following:

- Nausea.
- Hematologic toxic effects.
- Peripheral neuropathy.
- Orthostatic hypotension.
- Fatigue.

IMIDS:

IMiDs, or immunomodulatory drugs, are a group of oral drugs that are chemically similar to thalidomide. In the laboratory, they are more potent than thalidomide. In addition, preliminary clinical results suggest that the IMiDs appear to lack some of the more common side effects seen with thalidomide. The ones in advanced clinical trials include:

- Revlimid (formerly Revimid; lenalidomide, CC-5013)
- Actimid (CC-4047)

Like thalidomide, IMiDs are immunomodulatory agents. However, their precise mechanism of action is unknown and under investigation. IMiDs appear to have multiple actions, including both anticancer and anti-inflammatory activities.

IMiDs affect the immune system in several ways. They induce immune responses, enhance activity of immune cells, and inhibit inflammation. IMiDs appear to alter the levels of various cytokines and affect cells of the immune system. Reports from early studies show that IMiDs

Enhance the activation of T cells

- Enhance the activity of natural killer cells
- Enhance production of interleukin-2 (IL-2), a growth factor for T cells
- Inhibit inflammatory cytokines including

- Tumor necrosis factor-alpha (TNF-α)
- Interleukin 1-beta (IL-1β)
- Stimulate the production of interleukin-10 (IL-10), an antiinflammatory cytokine

In addition, the IMiDs inhibit angiogenesis through inhibition of vascular endothelial growth factor (VEGF), and this activity is not related to their immunomodulatory effects.

IMiDs are thought to affect multiple pathways in myeloma cells. IMiDs appear to have direct and indirect effects on myeloma cells, including the ability to

- Induce apoptosis (programmed cell death) of myeloma cells
- Inhibit myeloma cell growth
- Inhibit vascular endothelial growth factor (VEGF), thereby inhibiting angiogenesis
- Reduce adhesion of myeloma cells to bone marrow stromal cells

Additionally, in the laboratory, IMiDs appear to act synergistically with other antimyeloma agents and can kill myeloma cells that are resistant to conventional therapy.

In clinical trials conducted to date, IMiDs appear to have an improved safety profile over thalidomide. Significant sleepiness, constipation, or neuropathy — common side effects seen with thalidomide therapy — are much less frequent.

Revlimid entered clinical trials in 2000. Results from the Dana Faber Cancer Institute study were published recently.[50] Revlimid was used in doses of 5 to 50 mg/day to determine the maximal tolerated dose. Patients enrolled in the study had received an average of three prior regimens. Nineteen of 24 patients (79 percent) achieved stable disease or better (at least a 25% reduction in M protein). Seventy-one percent of patients experienced a ≥25 percent reduction in M protein levels, including 46% of patients who had previously received thalidomide, showing a lack of cross-resistance between thalidomide and Revlimid.

The Revlimid study at Arkansas included 15 patients. Eight patients experienced a >25% reduction in M protein and one patient achieved a complete response.

The drug had a manageable side effect profile, which included skin rash and some instances of reduced blood cell counts at higher doses. No significant sleepiness, constipation, or neuropathy was reported.

Results of the multicenter Phase II trial of Revlimid with or without dexamethasone in relapsed and refractory myeloma were quite encouraging. A total of 37% of patients with refractory or relapsed disease achieved a response with Revlimid alone. Preliminary results indicate that a total of 37% of patients receiving Revlimid alone achieved a response and the addition of dexamethasone resulted in a response in an additional 41% of patients.

Results of a randomized Phase II study of Revlimid as post-transplant salvage therapy were also reported. The study included 58 patients with advanced and refractory myeloma who received one of two dosing regimens of Revlimid: 25 mg/day x 20 days, followed by an 8-day rest period (1 treatment cycle) or 50 mg/day x 10 days, followed by an 18-day rest period (1 treatment cycle). Response rates were higher in patients receiving the more prolonged (25 mg x 20 day) dose schedule. Following the 8th cycle of treatment, 40% of patients in this arm of the study achieved a 50% or greater reduction in M protein compared to 15% of patients in the 50 mg x 10 day dose arm.

A Phase II open-label study of single-agent Revlimid in relapsed and refractory myeloma has completed enrolment and data are being collected. The multicenter study (Study 014), which is evaluating the safety and efficacy of the single agent, includes a total of 200 patients.

Phase III clinical trials of Revlimid, specifically designed to investigate the effectiveness of the drug in combination with dexamethasone in patients with relapsed or refractory myeloma, have completed enrolment and data are being collected.

At present, there are numerous Phase I/II and III trials on-going with Revlimid alone and in combination with other drugs in relapsed as well as newly diagnosed patient of myeloma.

Genasense

Genasense is an antisense drug being investigated for use as a treatment for myeloma and other cancers, such as melanoma, leukemia, lymphoma, and cancers of the lung, prostate, and colon. The agent is being used to increase the cancer-killing activity of standard anticancer therapy

In myeloma cells and other tumor cells, resistance to anticancer therapy is associated with the presence of a protein called Bcl-2. Genasense is a drug that turns off the production of the Bcl-2 protein, which may increase a tumor cell's sensitivity to therapy and ultimately, cause cell death.

Antisense drugs are small, chemically modified strands of DNA that are complementary to the specific mRNA (hence the term "anti") that codes for the protein (the "sense"). Antisense drugs are designed to bind to these mRNAs. Once bound to the mRNA, subsequent protein production is stopped.

Genasense is given as a continuous intravenous infusion using a portable pump, typically over the period of 5 to 7 days, followed by 1 to 3 weeks off. In clinical trials, a 3-week cycle is commonly used and may be repeated for many months.

Since 1995, more than 900 patients have been treated with Genasense. The most common side effects observed in clinical trials have been low-grade fever and fatigue. Thrombocytopenia has been observed in some patients who are also receiving other myelosuppressives.

Genasense received Orphan Drug status for the treatment of myeloma from the FDA in September 2001. Data from a Phase III multicenter trial of Genasense, in combination with dexamethasone, in patients with relapsed or refractory myeloma are being collected and analyzed.

Genasense is being evaluated in combination with the standard chemotherapy regimen VAD (vincristine, doxorubicin, and dexamethasone) in patients whose disease had previously progressed on VAD. The aim of this study is to see if the addition of Genasense can reverse the resistance to VAD therapy in these patients. The data suggest that this may be the case, as a number of partial and minor responses (70%) were seen in this heavily

pre-treated population. Median progression-free survival was 6 months and median overall survival had not yet been reached. The regimen was reported to be well tolerated. Other than fatigue, side effects from this regimen did not appear different from those expected from VAD chemotherapy alone.[51]

Arsenic Trioxide

Arsenic trioxide is a form of arsenic, a naturally occurring element that has been used for therapeutic purposes for more than 2000 years. Arsenic trioxide is being investigated as a treatment for myeloma, hematologic cancers, and various solid tumors. It is approved for the treatment of acute promyelocytic leukemia (APL).

Arsenic trioxide appears to have multiple antimyeloma effects. It has been shown to

- Inhibit the growth of myeloma cells in the laboratory
- Induce apoptosis of myeloma cells
- Block the ability of myeloma cells to "stick" to bone marrow stromal cells. It does this by inhibiting the production of adhesion molecules on the surface of both cell types. This, in turn, inhibits the secretion of interleukin-6 (IL-6), a growth factor for myeloma cells, by the stromal cells
- Inhibit angiogenesis by stimulating apoptosis of tumor-supporting endothelial cells and inhibiting the production of vascular endothelial growth factor (VEGF)

Ascorbic acid appears to enhance the activity of Arsenic trioxide against myeloma cells in the laboratory. The combination of the two agents appears to be effective in killing cells that are resistant to other drugs.

Arsenic trioxide is given as an intravenous infusion over a period of 1 to 4 hours. It is administered 2 to 5 days a week for various lengths of time, sometimes with time off the drug between cycles. It may be given in combination with dexamethasone and/or ascorbic acid.

The side effects seen with Arsenic trioxide therapy in myeloma patients appear to be somewhat different than those seen in patients with APL. In myeloma clinical trials, the most common side effects reported with Arsenic trioxide include leucopenia. These low counts can be managed with colony-stimulating factors. Other side effects that have been reported include fatigue, dyspnoea, pain, nausea, and vomiting.

Arsenic trioxide is currently being evaluated in a number of Phase II trials in relapsed and refractory myeloma, as well as prior to and following stem cell transplant.

The first Phase II study of Arsenic trioxide in relapsed and refractory myeloma included 14 patients who had relapsed or refractory disease and at least one autologous stem cell transplant. Patients received a 2-hour daily infusion of Arsenic trioxide at the same dose used in the treatment of APL (0.15 mg/kg for 60 days) for 60 days. Patients who responded received re-treatment 3 to 6 weeks after the first treatment. Altogether, three patients (21%) responded to a single infusion cycle; one patient had a greater than 75% reduction in M protein, one had a greater than 50% reduction, and one had a greater than 25% reduction.[52]

Arsenic trioxide is currently being evaluated in patients with relapsed or refractory myeloma in Phase II trials in combination with dexamethasone and/or ascorbic acid, which may enhance the efficacy of the agent. Arsenic trioxide is also being evaluated in combination with dexamethasone and ascorbic acid as maintenance therapy following bone marrow transplant, and in combination with ascorbic acid prior to bone marrow transplant.

Maintenance Therapy

Myeloma patients who respond to treatment show a progressive fall in the M-protein until a plateau is reached; subsequent treatment with conventional doses does not result in any further improvement. This has led investigators to question how long treatment should be continued. Three clinical trials considered the role of maintenance therapy; all found no improvement in survival.[53-55] In a single study[55], it was observed that maintenance therapy with MP prolonged the initial remission duration (31 months) compared to no maintenance treatment (23 months). There was no effect on overall survival, however, because the majority of patients who relapsed in the no maintenance arm responded again to MP, while those on maintenance MP did not respond to further treatment. Most therapists recommend continuing induction therapy for at least 12 months. Canadian group[55] suggests that induction chemotherapy be continued as long as the M-protein continues to fall; therapy can be discontinued after the M-protein reaches a plateau that remains stable for 4 months.

Maintenance interferon-alfa therapy has been reported in several studies to prolong initial remission duration.[56-59] While the impact of interferon maintenance on disease-free and overall survival has significantly varied among trials, a meta-analysis of 1,543 patients treated on 12 trials randomizing between interferon maintenance and observation indicated that interferon maintenance was associated with improved relapse-free survival (27% versus 19% at 3 years, P<.00001) and overall survival (12% odds reduction, P=.04).[60] In this population, toxic effects may be substantial and must be balanced against the potential benefits in response duration.[61] A study of 125 responding patients with first-line VAD induction randomized to maintenance corticosteroids at 10 mg or 50 mg on alternate days showed improved progression-free survival (14 months versus 5 months, P=.003) and overall survival (36 months versus 26 months, P=0.05) for the higher dose corticosteroids.[62]

Supportive Care in Myeloma

Advancement is supportive care of the myeloma patient has contributed significantly to the improvement in survival of patients with this cancer. The various elements of supportive care include: nutritional support, rapid correction of hyperviscosity, corrective of renal failure if present, treatment of infection, use of bisphosphonates, radiotherapy to sites of plasmacytoma or pathological factures or to painful bony lesions, orthopaedic intervention for factures and vertebral collapse (including vertebroplasty and kyphoplasty) and judicious use of haematopoietic growth factors (erythropoietin, granulocyte-colony stimulating factors) .

Bisphosphonate therapy

A randomized, double-blind study of patients with stage III myeloma showed that monthly intravenous pamidronate

significantly reduces pathologic fractures, bone pain, spinal cord compression, and the need for bone irradiation (38% skeletal-related events were reported in the treated group versus 51% in the placebo group after 21 months of therapy, P=0.015).[63] In addition, survival was increased (median survival was 21 months versus 14 months) in the patients receiving pamidronate and second-line or greater chemotherapy.

A randomized comparison of pamidronate versus zoledronic acid in 518 patients with multiple myeloma showed equivalent efficacy in regard to skeletal-related complications.[64]

Lytic lesions of the spine should be irradiated if they are associated with an extramedullary (paraspinal) plasmacytoma, if there is painful destruction of a vertebral body, or if there is computed tomography or MRI evidence of spinal cord compression.

Back pain caused by osteoporosis and small compression fractures of the vertebrae responds best to chemotherapy. Extensive radiation of the spine or long bones for diffuse osteoporosis may lead to prolonged suppression of hemopoiesis, and is rarely indicated. Bisphosphonates are useful for slowing or reversing the osteopenia that is common in myeloma patients.[63]

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