

A Concise Review  
of the Disease and  
Treatment Options

# Multiple myeloma

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## Mission Statement

**Dedicated to improving the quality of life of Myeloma patients while working towards prevention and a cure.**

This is one of a range of publications covering many aspects of living with Multiple Myeloma. Please contact the IMF (UK) for more details.

# Introduction

**This is an overview of the history of myeloma, a discussion of pathophysiology, clinical features plus treatment options. It is written for physicians and health professionals who treat myeloma, but perhaps not on a routine basis. The focus is primarily practical, founded upon the most recent research developments in the field.**

**It is hoped that the information will be helpful to physicians and patients alike.**

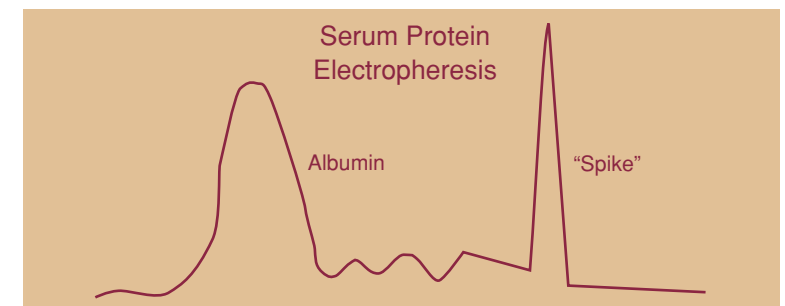
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# What is Myeloma?

Multiple myeloma (MM) is a malignancy of plasma cells. Plasma cells are antibody producing cells normally present in the bone marrow, but also occurring throughout the body wherever there is an immune response. Myeloma is usually called multiple myeloma because the malignant plasma cells, or myeloma cells, accumulate and produce areas of involvement in multiple areas of the bone marrow. The most commonly affected areas of bone marrow are in the spine and pelvis, plus the rib cage and skull. Sometimes only one bone marrow site is involved. This is a solitary plasmacytoma, also referred to as stage I myeloma. Occasionally, lesions occur in soft tissue outside of bone, frequently in the head and neck area. These are soft tissue plasmacytomas, which can also be referred to as myeloma stages I through III, depending upon the number of plasmacytomas.

Myeloma cells produce a monoclonal immunoglobulin which appears as a monoclonal "spike" in the serum and/or urine. See *Figure 1*:

Figure 1



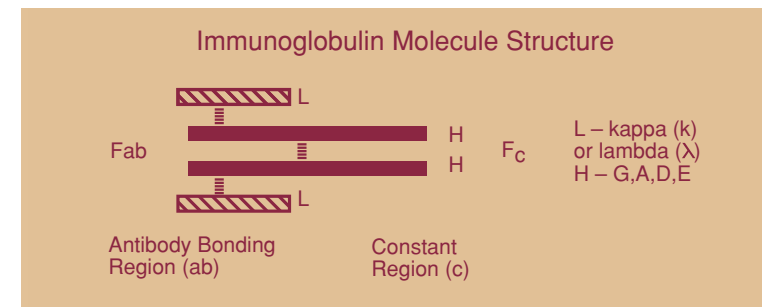
Although monoclonal “spikes” are typical of myeloma, they also occur in numerous other conditions including infections and auto-immune diseases (e.g. systemic lupus [SLE] and scleroderma). In the initial diagnosis it is crucial to exclude underlying disease processes as well as identify the definitive features of active myeloma such as bone destruction. Monoclonal Gammopathy of Undetermined Significance (MGUS) is a condition in which a monoclonal spike occurs, but there is neither active myeloma nor any underlying auto-immune disease, infection or other disease state. MGUS can persist with stable or very slowly changing levels of monoclonal protein for many years. If MGUS remains stable for two years, only 30% of patients will develop myeloma after a total of 10 years. Related conditions are: smoldering myeloma, in which the levels of monoclonal protein are higher than in MGUS, but still stable; and indolent myeloma in which there is evidence of myeloma (e.g. bone destruction), but a slowly changing picture over months to years.

The monoclonal spike in *Figure 1* contains the abnormal immunoglobulin molecule produced by the myeloma cell and released into the serum. *Figure 2* shows the structure of an immunoglobulin molecule consisting of two heavy chains (H) and two light chains (L) linked together as illustrated. Because of mutations in the immunoglobulin genes, myeloma proteins have an abnormal structure. Sometimes the molecule falls apart and myeloma cells produce light chains only (Bence Jones myeloma), heavy chains only (resulting in a rare condition called heavy chains disease) or molecular fragments. The F ab end of the molecule is usually defective so that the normal antibody function is lost. Myeloma therefore represents an exaggerated, but defective immune response. Unfortunately this expansion of myeloma cells suppresses the normal plasma cell reactions so that normal immunoglobulin levels are reduced. In rare cases (<1%), the myeloma cells are defective such that no spike is produced. This is non secretory myeloma which is otherwise similar to typical myeloma.

In Bence Jones myeloma the light chains pass from the serum into the urine so that the spike occurs in the urine not the serum. This is what can cause renal damage.

The clinical picture of multiple myeloma is varied. Nonetheless, it has a number of characteristic features including bone destruction with bone pain, elevated levels of monoclonal immunoglobulin in serum and/or Bence Jones proteins (light chains of immunoglobulins) in the urine, anaemia, elevated serum calcium and impaired renal function.

Figure 2



# History

## An annotated summary

- 1844-1850 First case descriptions of myeloma called “mollities and fragilitas ossium” (soft and fragile bones). The first patient, Thomas Alexander McBean, was diagnosed in 1845 by Dr. William Macintyre, a Harley Street consultant in London. The unusual urine problem he discovered was fully investigated by Dr. Henry Bence Jones who published his findings in 1848. In 1846, Mr. John Dalrymple, a surgeon, noted and published that the diseased bones contained cells subsequently shown to be plasma cells. Dr. Macintyre published the full details of this case of Bence Jones myeloma in 1850. It has been noted that Dr. Samuel Solly published a case of myeloma (Sarah Newbury) in 1844.
- 1873 Rustizky introduced the term “multiple myeloma” to designate the presence of multiple plasma cell lesions in bone.
- 1889 Otto Kahler published a detailed clinical description of multiple myeloma, “Kahler’s disease”.
- 1890 Ramon y Cajal provided the first accurate microscopic description of plasma cells.
- 1900 Wright discovered that multiple myeloma cells are plasma cells.
- 1903 Weber noted that myeloma bone disease (lytic lesions) shows up on X-rays.
- 1909 Weber suggested that plasma cells in the bone marrow actually produce the myeloma bone destruction.
- 1930’s The routine diagnosis of myeloma remained difficult until the 1930’s when bone marrow aspirates were first used on a larger scale. The development of the ultracentrifuge and serum/urine protein electrophoresis improved both screening and diagnosis.
- 1953 Immunoelectrophoresis was introduced to allow exact identification of the monoclonal myeloma proteins. (Immunofixation has since been introduced as a more sensitive method.)

- 1956 Korngold and Lipari noted that Bence Jones proteins are related to normal serum gammaglobulin as well as abnormal serum proteins. In their honour, Bence Jones proteins are called kappa (k; Korngold), and lambda (l; Lipari).
- 1958 Discovery of sarcolysin. For the first time treatment was possible. From sarcolysin, melphalan (Alkeran) was derived.
- 1961 Waldenstrom emphasised the importance of the differentiation between monoclonal and polyclonal gammopathies. He associated IgM monoclonal proteins with macroglobulinemia, as distinct from myeloma.
- 1962 First report of successful treatment of myeloma with melphalan (Alkeran) by Bergsagel.
- 1964 First report of successful treatment of myeloma with cyclophosphamide (Cytosan) by Korst. Results with cyclophosphamide proved to be similar to results with melphalan.
- 1969 Melphalan combined with prednisone (MP), by Alexanian, was shown to give better results than melphalan alone.
- 1975 Durie/Salmon staging system for myeloma introduced. Patients classified to assess benefits of chemotherapy at different disease stages (I, II, III, A or B).
- 1976-1992 Various combinations of chemotherapy agents tried, including the M2 regimen (VBMCP), VMCP-VBAP, and ABCM, with some indication of superiority versus MP. However, in 1992, a comparative meta-analysis (Gregory) showed equivalent results for all combinations.
- 1979-80 Labelling index (growth fraction analysis) first introduced as a test in myeloma and related diseases. Stable remission or plateau phase of myeloma identified as a period when the myeloma cell growth fraction (L1%) is zero %.
- 1982 Twin transplants performed by Fefer and Osserman as treatment for myeloma.
- 1983 First use of serum B2 microglobulin as a prognostic test (Bataille and Durie).
- 1984 VAD chemotherapy first introduced by Barlogie and Alexanian.
- 1984-1986 First reports of allogeneic transplants in myeloma by various investigators.

- 1986-1996 Large numbers of studies evaluating high dose therapy with autologous bone marrow or stem cell rescue by various investigators. Both single (McElwain) and double (Barlogie) transplant procedures introduced.
- 1996 First, and thus far only, randomised study indicating possible benefit of high dose therapy with bone marrow transplant support versus standard chemotherapy (Attal). As yet no meta-analysis or other larger comparative studies performed.

Of the various chemotherapies introduced since 1958, nothing is clearly superior to MP. The combination of melphalan plus prednisone gives an objective response in 50-60% of the patients and clinical benefit in another 15-20%. Many other polychemotherapy schemes have been tried since 1962 without dramatically better results, and MP is still the gold standard of therapy. Although high dose therapy (e.g. high dose IV melphalan) can produce better remissions in symptomatic patients with advanced active disease, the overall impact on survival remains to be fully assessed.

Research is on-going utilising high dose chemotherapy with stem cell transplantation followed by use of cytokines such as alpha interferon and/or IL2. Other cytokines of interest include IL-1β, IL3, IL4, IL6, IL10, IL12, erythropoietin, GM-CSF and G-CSF.

# Epidemiology and Pathophysiology

## Clinical Symptoms

## Staging and Prognostic Factors

## Definition of Clinical Response

## Treatment

### Epidemiology

There are approximately 3,000 new cases of myeloma in the UK each year representing 15% of blood cancers and 1% of all types of cancer. The incidence varies from country to country from a low of 1/100,000 in China to approximately 4/100,000 in most Western industrialised countries. The male/female ratio is 3:2. The incidence rises with age. Better diagnostic techniques and the higher average age of the general population may in part explain the rising incidence over the last several decades. A trend toward more frequent myeloma in patients under age 55 implies important environmental causative factors in the past 3-4 decades.

### Pathophysiology

The uncontrolled growth of myeloma cells has many consequences including skeleton destruction, bone marrow failure, increased plasma volume and viscosity, suppression of normal immunoglobulin production, and renal insufficiency. Nonetheless, the disease can remain asymptomatic for many years, as noted in the discussion of MGUS. In the symptomatic phase, the most common presenting complaint is bone pain.

The serum and/or urine M protein is elevated and typically rising at the time of diagnosis. Please note: M is used for Monoclonal, Myeloma, Monoclonal immunoglobulin, M-component (all are not quite identical but are used somewhat synonymously). Treatment improves the clinical situation in about 75% of patients. It is important to emphasise that multiple periods of remission and relapse can occur. The overall disease course is as illustrated in *Figure 3*:

Figure 3

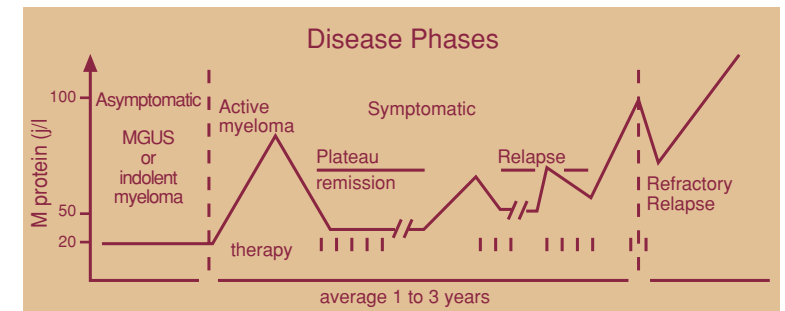


Table 1 summarises the pathophysiology of myeloma in schematic form:

Table 1

Schema of Pathophysiology	
<b>Skeletal findings</b>	<ul style="list-style-type: none"> <li>solitary or multiple osteolytic lesions</li> <li>diffuse osteoporosis</li> </ul>
<b>Associated effects of bone destruction</b>	<ul style="list-style-type: none"> <li>elevated serum calcium</li> <li>hypercalciuria</li> <li>loss of height</li> </ul>
<b>Extra skeletal myeloma</b>	<ul style="list-style-type: none"> <li>soft tissue involvement, most commonly in head/neck area, e.g. nasopharynx; also liver, kidney and other soft tissue</li> </ul>
<b>Peripheral blood</b>	<ul style="list-style-type: none"> <li>anaemia</li> <li>abnormal clotting</li> <li>leukopenia</li> <li>thrombocytopenia</li> <li>plasma cell leukemia</li> <li>circulating monoclonal B lymphocytes (precursors of myeloma cells)</li> </ul>
<b>Plasma protein changes:</b>	<ul style="list-style-type: none"> <li>hyperproteinemia</li> <li>hypervolemia</li> <li>monoclonal immunoglobulins (IgG, IgD, IgA, IgM, IgD, light chains)</li> <li>amyloidosis</li> <li>narrowed anion gap (low serum sodium)</li> <li>elevated serum B2-microglobulin</li> <li>decreased serum albumin</li> <li>elevated serum IL6 and C-reactive protein (CRP)</li> </ul>
<b>Kidney abnormalities:</b>	<ul style="list-style-type: none"> <li>proteinuria, casts without leukocytes or erythrocytes</li> <li>tubular dysfunction with acidosis</li> <li>uremia (kidney failure)</li> </ul>

Myeloma produces different types of monoclonal protein. The most common is IgG and the rarest IgE. See Table 2. Each type is associated with slightly different patterns of disease. For example, IgA myeloma is more commonly associated with disease outside bone (extraskelatal disease) whereas, IgD myeloma is more commonly associated with plasma cell leukaemia and renal damage.

Table 2 shows the percentages of different types of myeloma:

Table 2

Types of Monoclonal Proteins (M-components)	Percentages/Totals	
Serum types:		
IgG	52	
IgA	21	75%
IgD	2	
IgE	<0.01	
Urine (Bence Jones, or light chains only) types k and l		11%
Heavy chains (G or A) only	<1	
2 or more monoclonal paraproteins	<1	2%
No monoclonal paraprotein	1	
*IgM		12%
<b>Total</b>		<b>100%</b>
*IgM (rarely myeloma), typically associated with Waldenstrom's macroglobulinemia.		
<i>Source: Data on 1,827 MM patients collected and analysed by Pruzanski and Ogryzlo, 1970.</i>		

Some of the most striking changes in pathophysiology result from the elevated serum M-component. The plasma volume rises due to the elevated total serum protein content. It can cause pseudo hyponatraemia (low serum sodium) and narrowed anion gap. High concentrations of myeloma protein can give a clinical picture called hyperviscosity syndrome.

Diffuse precipitation of the myeloma protein in the kidney tubules or urine collecting systems, combined with cast formation, can result in impaired kidney function (myeloma kidney). Many other factors, such as infections, hypercalcaemia, and nephrotoxic drugs, can impair renal function. Myeloma patients with renal impairment must avoid or limit the use of drugs which may further impair renal function. Sometimes, myeloma is preceded by a type of Bence Jones-MGUS reflected by kidney abnormalities presenting with, for example, adult Fanconi syndrome. Fanconi syndrome is a selective kidney tubular defect with leakage of amino acids and phosphates in the urine which can cause metabolic bone disease.

### Clinical symptoms

The majority of myeloma patients (about 70%) present with pain of varying intensity, often in the lower back or ribs. Sudden severe pain can be a sign of fracture or collapse of a vertebral body. General malaise and vague complaints are frequent. Significant weight loss is rare.

Both neutropenia and hypogammaglobulinemia increase the likelihood of infections. Although pneumococcal pneumonia is the "classical" infection associated with myeloma at presentation, other bacteria, such as streptococci and staphylococci, are now frequently isolated. Haemophilus infection and herpes zoster infections also occur.

Hypercalcaemia, present in 30% of the patients at diagnosis, causes tiredness, thirst and nausea. Precipitation of calcium salts can result in deterioration of kidney function. Hyperviscosity, due to high myeloma protein levels, can cause problems such as bruising, nose bleeding, hazy vision, headaches, gastrointestinal bleeding, sleepiness, and a variety of ischaemic neurological symptoms. These last are caused by reduced blood and oxygen supply to the nerve tissue. Hyperviscosity occurs in <10% of myeloma patients, it affects about 50% of patients with Waldenstrom's macroglobulinemia (IgM paraprotein or M-component). Increased bleeding is often accentuated by thrombocytopenia, in addition to the binding of monoclonal proteins to clotting factors and/or platelets.

Neurologic involvement can result in specific problems depending on location. Particularly common problems are spinal cord compression, meningitis and carpal tunnel syndrome. Although the first two are due to plasma cell tumor formation or unfiltration, carpal tunnel syndrome is usually due to amyloid deposition, (deposition of Bence Jones proteins in a special beta pleated form).

## Staging and Prognostic Factors

### Staging:

Prognosis in myeloma is determined by both the number and specific properties of myeloma cells in a given patient. These specific properties include growth rate (fraction), production rate of monoclonal proteins and production or non production of various cytokines and chemicals which damage or significantly impair other tissue, organ or bodily functions. In 1975, the Durie/Salmon staging system was developed. This system brings together the major clinical parameters in correlation with measured myeloma cell mass (the total number of myeloma cells in the body). See Table 3:

Table 3

### Basic Classification

**Stage I low cell mass (<0.6 X 10<sup>12</sup> cells/m<sup>2</sup>)**

**Stage II intermediate cell mass (0.6 – 1.2 X 10<sup>12</sup> cells/m<sup>2</sup>)**

**Stage III high cell mass (>1.2 X 10<sup>12</sup> cells/m<sup>2</sup>)**

Durie and Salmon Staging System:	
Criteria	Measured myeloma cell mass (cells x 10 <sup>12</sup> /m <sup>2</sup> )
<p><b>Stage I:</b> All of the following:</p> <ul style="list-style-type: none"> <li>Haemoglobin value &gt; 100 g/l</li> <li>Serum calcium value normal or &lt; 2.60 mmol/l</li> <li>Bone X-ray, normal bone structure (scale 0) or solitary bone plasmacytoma only</li> <li>Low M-component production rates</li> <li>IgG value &lt; 50 g/l</li> <li>IgA value &lt; 30 g/l</li> <li>Urine light chain M-component on electrophoresis</li> </ul>	<0.6 (low)
<p><b>Stage II:</b> Fitting neither stage I nor stage III</p>	0.6-1.20 (intermediate)

Table 3 (continued)

<b>Stage III:</b> One or more of the following:	
Haemoglobin value < 85 g/l	
Serum calcium value > 3.00 mmol/l	
Advanced lytic bone lesions (scale 3)	
High M-component production rates	> 1.20 (high)
IgG value > 70 g/l	
IgA value > 50 g/l	
Urine light chain M-component on electrophoresis > 12 g/24 h	
Subclassification (A or B)	
A Relatively normal renal function (serum creatinine value < 170 umol/l)	
B Abnormal renal function (serum creatinine value ≥ 170 umol/l)	
<i>Examples:</i>	
Stage IA Low cell mass with normal renal function	
Stage IIIB High cell mass with abnormal renal function	

The Durie/Salmon staging system continues to be used worldwide. Since 1975, several new parameters have been discovered. Among these are: serum B2 microglobulin, a measure of disease activity; as well as labeling index (LI%), a specific indicator of growth rate. Numerous investigators have evaluated these and other prognostic factors. For example, Greipp *et. al.* published in *Blood* (vol. 72, pp. 219-223, 1988) a staging classification using both of these parameters together. They used a cutoff for the B2 microglobulin of 2.7 u/ml and 0.4% for the plasma cell labelling index.

In 1991, Durie presented and published a variation of the scheme which also uses these two parameters. See *Table 4*:

Table 4

<b>Stage:</b>		
<b>I</b>	low risk	both LI%*/SB2m low*
<b>II</b>	average risk	one parameter high/low
<b>III</b>	high risk	both LI%/SB2m high
*cutoffs:	0.4% for plasma cell LI%	
	4 u/ml for plasma cell SB2 m	

This staging makes it possible to categorise patients and select optimal therapy. The cutoff for SB2m of 4 u/ml is more realistic than 2.7 to encompass the whole range of myeloma patients. For most laboratories 2.7 is a normal value.

**Prognostic Factors:**

The staging system in *Table 4* illustrates two factors which affect prognosis in myeloma. At the moment there are 5 important factors:

1. B2 microglobulin
2. The plasma cell labelling index
3. C-reactive protein, which directly corresponds with activity of IL6, an important growth factor for multiple myeloma
4. Serum creatinine (part of the sub-classification A/B in the Durie/Salmon staging system)
5. The age of the patient at diagnosis

A subsequent proposal by Bataille *et. al.* makes use of CRP and B2 microglobulin. This scheme, first presented during the International Workshop on Multiple Myeloma in Turin in April 1991, and later published in *Blood* (1992, vol. 80, no. 3), illustrates the benefit of using this new prognostic factor combination. This derived classification is shown in *Table 5*:

Table 5

<b>Risk Groups</b>	<i>Low</i>	Both CRP/B2m low*
	<i>Average</i>	One parameter high/low
	<i>High</i>	Both CRP/B2m high
<i>Using CRP and B2m with cutoff values of 6</i>		

In time, other prognostic factors will be introduced including molecular abnormalities (e.g. oncogene/anti oncogene mutations) and abnormalities on FISH evaluation of bone marrow. Such testing remains expensive and not routinely available. It is reasonable to anticipate the introduction of tests which not only reflect prognosis, but can also help direct treatment selection.

### Definition of Clinical Response

There are several methods to classify response to treatment. A frequently used method is illustrated in *Table 6* :

Table 6

<b>1. Complete Response (CR)</b>	<b>Standard Definition (SWOG*):</b> ≥75% reduction in serum myeloma protein level (>90% in urine).
<b>2. True Complete Response</b>	<b>More Stringent Definition:</b> Elimination of M-component from serum and urine plus no evidence of myeloma in the bone marrow.
<b>3. Partial Response (PR)</b>	≥50% <75% regression
<b>4. Objective Response (OR) or Stable Disease</b>	≥25% <50% regression
<b>5. No Response (NR)</b>	<25% regression or progressive disease

*\*This has been a long standing definition used by SWOG. (South Western Oncology Group)*

Many variations of this classification are in use. The improvements in M-component must also be associated with evidence of clinical improvement (reduced bone pain, improved anaemia etc.). With the possible exception of True Complete Response, see *Table 6 #2*, it is important to keep in mind that a higher percent regression does not necessarily confer a better survival. When there is residual disease, the characteristics of the remaining drug resistant myeloma cells determine the outcome. The fraction of resistant myeloma cells is primarily dependent upon the pre-treatment tumor burden or stage.

Responding patients go from a high risk to a lower risk status until, ideally, no signs of MM are left or they achieved a stable plateau phase, but with measurable residual disease. The time required to achieve the plateau phase is variable, ranging from 3-6 months (rapid response), to 12-18 months (slow response). Refer to *Figure 3*:

### Treatment

The history section provides an overview of the evolution of currently used treatments. Since melphalan was first introduced in 1962, various combination chemotherapy regimens have been utilised and attempts made to improve outcomes using high dose chemotherapy regimens with bone marrow transplant (BMT) or stem cell rescue. There is as yet no consensus as to the best way to manage MM, however, the following will provide some guidelines.

#### 1. The decision to treat

Since myeloma is not curable, the first and most important decision is to ascertain if therapy is required. Patients with Monoclonal Gammopathy of Undetermined Significance (MGUS) and smoldering myeloma should be observed closely rather than treated. There are currently no therapies that can enhance the immune regulation of early myeloma or reduce the likelihood of disease activation. However, research options are available, (e.g. anti-idiotypic vaccines).

Treatment is recommended when the M-component is increasing and/or clinical problems have emerged or are imminent. Problems sufficient to require treatment include bone destruction (lytic lesions and/or osteoporosis), renal insufficiency, reduced blood counts (e.g. anaemia, neutropenia), elevated blood calcium, nerve damage or other significant organ or tissue damage caused by myeloma or myeloma protein. The overall goals of treatment are to address specific problems and to achieve general control of the disease.

## 2. Types of treatments

### A. Chemotherapy

A summary of myeloma treatment options is provided in *Table 7*. The treatment options include induction chemotherapy, higher dose chemotherapy and supportive care therapy. The most commonly used drugs are listed in *Table 8*. Since first introduced in 1962, melphalan has remained the best single agent for the management of MM. The majority of patients respond to treatment with this agent particularly when combined with prednisone.

Table 7

Overall Summary of Myeloma Treatment Options	
1. Chemotherapy	
2. High dose therapy with transplant	
3. Radiation	
4. Alpha interferon	
5. Erythropoietin	
6. Bisphosphonates	
7. Other supportive care aspects	<ul style="list-style-type: none"> <li>• emergency care e.g. dialysis, plasmapheresis, surgery or radiation</li> <li>• pain medication</li> <li>• antibiotics</li> <li>• growth factors</li> <li>• brace/corset</li> <li>• exercise</li> <li>• diet</li> </ul>
8. New drugs/strategies	<ul style="list-style-type: none"> <li>• Reversal of multi-drug resistance (e.g. PSC-833)</li> <li>• new cytokines (e.g. IL-6, 2, 4)</li> <li>• new vaccines (e.g. anti-idiotypic)</li> <li>• New chemotherapy drugs</li> </ul>

(i) Melphalan/Prednisone (MP) and Cytoxan/Prednisone (CP)

The MP combination is the most frequently used. Sixty percent of patients have an objective response reflected by a 50% improvement in the myeloma protein level plus improvement in blood count and other blood test results, along with improvement in the various symptoms of the disease, such as bone pain and fatigue. Cytoxan can be substituted for melphalan since it has a similar anti-myeloma activity. Cytoxan is less toxic to normal bone marrow stem cells and can be considered in patients who may be candidates for future stem cell transplantation. It has more immediate side effects than melphalan including GI toxicity, such as nausea.

Table 8

Most commonly used drugs		
Drug Name	Other Treatment Name	Comments
• Melphalan* (M)**	Alkeran® (by mouth or IV)	Best single agent for treatment.
• Cyclophosphamide*	Cytoxan® (by mouth or IV)	Similar efficacy to melphalan, (C or CY**) but more GI and GU toxicity. Less bone marrow stem cell injury.
• BCNU* (B)**	Bis-chloro-Nitrosurea® (IV only)	Similar to melphalan and Cytoxan, but less effective and more toxic, especially bone marrow and lung toxicity.
• Prednisone (P)**	Prednisolone® (similar) (usually by mouth)	Directly active, works well with M, C and B above. Does not produce suppression of bone marrow.

Table 8 (continued)

<ul style="list-style-type: none"> <li>• Dexamethasone (D)**Decadron® (by mouth or IV)</li> </ul>		Similar to prednisone but more potent. Also more severe side effects.
<ul style="list-style-type: none"> <li>• Vincristine (V or O)** Oncovin® (IV only)</li> </ul>		Modest activity, frequently used as part of combination regimens (e.g. VAD).
<ul style="list-style-type: none"> <li>• Doxorubicin (A)** Adriamycin® (IV only)</li> </ul>		Modest activity, used in combinations (e.g. VAD, ABCM, VMCP-VBAP).
<ul style="list-style-type: none"> <li>• Busulphan* (B or BU)** Myleran® (by mouth or IV)</li> </ul>		Similar activity to melphalan and Cytoxan usually part of high dose therapy with transplant (e.g. BU/Cy regimen).
<ul style="list-style-type: none"> <li>• VP – 16 (E) Etoposide® (IV)</li> </ul>		Modest activity – used alone or in combination.
<ul style="list-style-type: none"> <li>• Cis-platinum (CP) Platinol® (IV)</li> </ul>		Minimal activity, occasionally used.

\* These are alkylating agents.  
 \*\* Common abbreviations

(ii) More Complex Combination Schedules

Since the mid sixties many combinations and permutations of the most commonly used drugs have been tried. Combinations for which there is a suggestion of additional benefit versus MP or CP have been listed in Table 9. The M2 protocol was developed at Memorial Sloan-Kettering Cancer Center in New York. A few studies have suggested that there is a higher response rate and an overall better outcome using the M2 protocol versus MP. For example, in a recent analysis from the Eastern Cooperative Oncology Group (ECOG), the overall survival of patients treated with M2 proved to be identical to those receiving MP. However, the survival at five years was superior in the M2 protocol arm. The toxicity and the costs are significantly greater with the M2 combination strategy. Similar information has been gathered with the VMCP/VBAP and ABCM protocols. These have shown some indications of superiority versus MP, however they are more toxic and expensive.

Table 9

Frequently used combinations	
Combination	Comments
<ul style="list-style-type: none"> <li>• MP</li> <li>• CP</li> <li>• VBMCP (M2 protocol)</li> </ul>	<ul style="list-style-type: none"> <li>• Standard combination for initial therapy.</li> <li>• Alternative to MP.</li> <li>• Combination often used in eastern USA. Proponents suggest better response and survival versus MP.</li> </ul>
<ul style="list-style-type: none"> <li>• VMCP / VBAP (alternating)</li> </ul>	<ul style="list-style-type: none"> <li>• Combination developed by SWOG and often used in western USA. More toxic with minimal increased benefit as is true for M2.</li> </ul>
<ul style="list-style-type: none"> <li>• ABCM</li> </ul>	<ul style="list-style-type: none"> <li>• Combination used in Europe especially UK. Little extra benefit versus MP.</li> </ul>
<ul style="list-style-type: none"> <li>• VAD</li> </ul>	<ul style="list-style-type: none"> <li>• Most commonly used alternative to MP, especially if myeloma is aggressive, if there is renal insufficiency or if high dose therapy with transplant is planned.</li> </ul>
<ul style="list-style-type: none"> <li>• D or MD</li> </ul>	<ul style="list-style-type: none"> <li>• D alone or combined with M (MD) or C (CD) can be used as alternative to VAD. Avoids need for four day infusion.</li> </ul>

Proponents of these combination schedules, those who have used them for many years, continue to recommend them because the outcome is at least as good as with MP and there is a suggestion that it may even be slightly better. The current trend is to use MP or CP as a first choice and reserve the more complex combinations as a back up approach for patients who fail to have a satisfactory response.

A confusing aspect of myeloma treatment has been the discovery that more dramatic reductions in the amount of myeloma, as reflected by the level of myeloma protein in the serum and/or urine, does not necessarily translate into longer remissions or longer overall survival. The major factor which determines outcome is the intrinsic drug sensitivity or resistance of the myeloma. Since no current therapy eradicates all the myeloma cells, the characteristics of the cells left following initial chemotherapy are of particular importance. A few aggressive residual myeloma cells can potentially cause more trouble than a larger number of inactive cells.

#### *(iii) VAD Chemotherapy*

The VAD protocol, first introduced in 1984, has become a popular alternative to MP or CP induction. The major reason for this is not that it produces better overall outcome, but because it can produce response without injuring the normal bone marrow stem cells. It is a particular advantage in patients who are scheduled to have high dose therapy with transplantation. In addition the high dose dexamethasone, which is part of the VAD, can be very helpful in patients with initial, very aggressive disease and/or renal failure who need rapid disease control to improve urgent medical problems. A simple alternative is dexamethasone alone. This can dramatically improve the clinical situation without reducing blood count levels and without the need for insertion of an intravenous catheter followed by a four day infusion.

#### *(iv) Monitoring of Response*

Table 10 lists tests required to carefully monitor therapy response.

Table 10

#### **Required testing to monitor Myeloma**

- Blood tests
  - Routine blood counts
  - Chemistry panel
  - Liver function tests
  - Myeloma protein measurements\*
  - Serum B2 microglobulin
  - C – reactive protein
  - Peripheral blood labelling index
  - Serum erythropoietin level
- Urine
  - Routine urinalysis
  - 24 hour urine for Bence Jones protein and albumin plus creatinine clearance.
- Bone evaluation
  - skeletal survey by X-ray
  - MRI/CT scan for special problems
  - MIBI/other scans, if required
  - Bone density measurement (DEXA SCAN) as baseline and to assess benefit of bisphosphonates
- Bone Marrow
  - Aspiration and biopsy for diagnosis and periodic monitoring
  - Special testing to assess prognosis e.g. chromosomes / immunotyping / LI %
- Other testing depending upon special circumstances:
  - amyloidosis
  - neuropathy
  - renal or infectious complications

\* Serum protein electrophoresis plus quantitative immunoglobulins

The most important aspect is to know if the symptoms at presentation have improved. One must assess blood count levels, chemistry results, and particularly levels of myeloma protein in the serum and urine. Important markers of myeloma activity are the serum beta2 microglobulin, the C-reactive protein plus the labelling index in the peripheral blood and/or bone marrow. It is important to have a periodic 24 hour urine test to exclude the possibility of Bence Jones escape. This is a situation in which the urine protein may increase, even though the serum protein level has improved. Follow up X-rays of the bones are important to exclude possible new bone involvement. Additional scanning, including MRI and CT, may be necessary to more closely evaluate the status of the bones. DEXA scan can be used to quantitate base line and follow up bone density.

### B. High Dose Therapy with Transplant

For the past ten years, a major new strategy has been the use of high dose alkylating agents such as melphalan, cytoxan or busulphan either alone or in combination. Following high doses of these alkylating agents, rescue is required in the form of either growth factors for intermediate doses, or stem cell rescue for high doses. Rescue can be in the form of an autologous transplant, in which the patient's own normal stem cells are utilised, or in the form of an allogeneic/syngeneic transplant, in which HLA identical or twin donor stem cells are utilised. The possible advantages and disadvantages of these three types of transplants are summarised in *Table 11*. The benefit of all strategies is that, with the administration of high dose chemotherapy, a more dramatic myeloma cell kill and remission can be achieved in a majority of patients.

Table 11

High dose therapy	
Advantages	Disadvantages
<i>Single Autologous Transplant</i>	
<ul style="list-style-type: none"> <li>• 50% excellent remissions.</li> <li>• At least as good as standard therapy regarding overall survival and probably better for some patients</li> <li>• Basis for strategies to produce true remission or long term cure.</li> </ul>	<ul style="list-style-type: none"> <li>• Relapse pattern similar to standard chemotherapy</li> <li>• More toxic and expensive</li> <li>• Patients who benefit from transplant not clearly identified.</li> <li>• Interferon maintenance required.</li> </ul>
<i>Double Autologous Transplant</i>	
<ul style="list-style-type: none"> <li>• Same as single.</li> </ul>	<ul style="list-style-type: none"> <li>• As yet no clear benefit versus single transplant.</li> <li>• Much more toxic and expensive versus single.</li> </ul>
<i>Allogeneic Transplant</i>	
<ul style="list-style-type: none"> <li>• No risk of contamination of marrow/stem cells with myeloma.</li> <li>• Possible graft versus myeloma effect to prolong remission.</li> </ul>	<ul style="list-style-type: none"> <li>• Even for HLA identical siblings significant risk of early complications and even death (at least 10 – 15% chance).</li> <li>• Risk of complications unpredictable.</li> <li>• Procedure restricted to age ≤ 55 years.</li> <li>• Even more toxic and expensive versus autologous.</li> </ul>
<i>Twin Transplant</i>	
<ul style="list-style-type: none"> <li>• No risk of myeloma contamination in transplanted cells.</li> <li>• Much less risky than allogeneic transplant.</li> </ul>	<ul style="list-style-type: none"> <li>• No graft versus myeloma effect.</li> <li>• Need identical twin and age ≤ 55 years.</li> </ul>

Currently 50% of patients can achieve complete response with high dose therapy, see *Table 6*. The most immediate features of myeloma are reversed and the patient is without symptoms of the disease. Excellent clinical remission is the major advantage. A crucial disadvantage is that the disease is still not cured. Relapse occurs, with a similar time pattern to that observed after standard chemotherapy. Relapse can be delayed by the use of interferon as a maintenance after the high dose approach. The benefit is greatest for patients who achieve a complete remission with the high dose strategy.

As far as the overall benefit with high dose therapy versus MP, there is only one randomised study that compared high dose treatment with conventional therapy. In this study, there is a significant advantage in terms of achieving remission, as well as a trend towards improved survival, with the high dose approach. This study was predominantly restricted to patients with advanced aggressive disease under the age of 60. The major concern about high dose therapy is that only a fraction of patients may need and benefit from the high dose approach. We don't yet know which patient population needs this approach. A recent analysis from Italy suggests that the major sub population needing and benefiting from high dose therapy is the group of patients under the age of 60, with stage III disease, who have very aggressive disease as reflected by a high pre-treatment bone marrow labelling index. The immediate question is whether patients with stage I, II or III, with less aggressive features, need or benefit from high dose strategies.

#### *(i) Allogeneic and Twin Transplants*

The relative advantages and disadvantages of allogeneic or twin transplants are listed in *Table 11*. Such transplants are limited to patients who either have a twin or an HLA identical brother or sister. The patient also should be under age 55. With allogeneic transplant, the up front risks are quite daunting in that at least 20 to 30% of patients are at risk from early death because of complications related to the transplant. For some reason, in patients with MM, risks of complications remain high despite intensive supportive care at even the most experienced treatment centres. The risks with twin transplants are much less, and can usually be recommended for young patients with an identical twin. None of these procedures is curative. In all but a rare few patients, relapse supervenes.

### **C. Radiation Therapy**

Radiation therapy is an important modality of treatment for myeloma. For patients with severe local problems such as bone destruction, severe pain and/or pressure on nerves or the spinal cord, local radiation can be dramatically effective. The major disadvantage is that radiation therapy permanently damages normal bone marrow stem cells in the area of treatment. Wide field radiation encompassing large amounts of normal bone marrow should be avoided. A general strategy is to rely on systemic chemotherapy to achieve overall disease control, limiting the use of local radiation therapy to areas with particular problems.

Whole body radiation or sequential radiation of half of the body can be used as part of an overall strategy for high dose therapy with transplant and/or in the management of relapsing refractory disease. It is not yet clear whether whole body radiation adds to alkylating agent therapy for patients receiving transplant. In patients with refractory disease, sequential hemibody radiation can be used to temporarily control the disease. This is rarely successful for very long, particularly in patients with aggressive, active myeloma. There is also the disadvantage that wide field radiation destroys the normal bone marrow and makes it difficult if not impossible to use other treatment options following this approach.

### **D. Alpha Interferon**

Alpha Interferon is important in MM since it is the only agent shown to prolong remission achievable with standard or high dose therapy. For the past 15 years many investigators have evaluated the efficacy of interferon. Conflicting results have been obtained, but a small benefit in the prolongation of remission has been observed. The benefit is only 10 to 15% in terms of prolongation of remission and survival. Differences of 10 to 15% (e.g. 6-9 months) are hard to prove in clinical studies. Ongoing studies include evaluation of interferon with initial chemotherapy and the combination of alpha interferon with a variety of agents such as dexamethasone or IL-2 for maintenance. The use of alpha interferon has to be individualised, balancing potential benefits with potential side effects, expense and inconvenience. Most investigators think that alpha interferon has a definite although small role in the management of myeloma.

## E. Erythropoietin

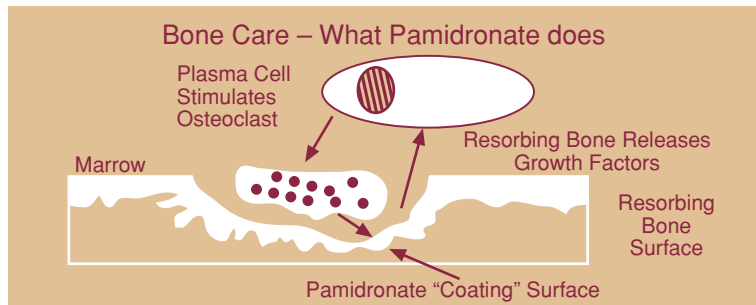
Erythropoietin is a naturally occurring hormone now available through genetic engineering techniques. Erythropoietin is administered to improve the haemoglobin level in patients who have persistent anaemia.

Erythropoietin injections (e.g. 10,000 i.u three times per week) can show dramatic benefit in the level of haemoglobin and in performance status. It should be strongly considered in patients who have persistent anaemia. Erythropoietin should only be continued in patients showing clear benefit.

## F. Bisphosphonates

Bisphosphonates are a class of chemicals which bind to the surface of damaged bones in patients with MM. This binding inhibits the ongoing bone destruction and can improve the chances of bone healing and recovery of bone density and strength. A recent randomised study utilising the bisphosphonate Pamidronate showed particular benefit in patients responding to ongoing chemotherapy. It is currently recommended that Pamidronate be used as an adjunctive measure in MM patients who have bone problems. Please see *Figure 4*:

Figure 4



Other bisphosphonates are available including Clodronate, an oral formulation in use in Europe for the treatment of MM. Several new bisphosphonates are in clinical trial. Zoledronate, a bisphosphonate generating great interest, is possibly one thousand times more potent than Pamidronate. Zoledronate could produce dramatic benefit in terms of improved bone healing. It is hoped that combining the new bisphosphonates with other agents can dramatically affect the management of bone disease in myeloma patients.

## G. The Use of Antibiotics

Infections are a common and recurrent problem in patients with MM. A careful strategy for infection management is required. Antibiotic therapy should be instituted immediately if active infection is suspected. Use of preventative or prophylactic antibiotics with recurrent infection is controversial. The continuation of prophylactic antibiotics can increase the chance of antibiotic resistance, but it can also reduce the chance of recurrent infective complications.

A recent comparative study showed benefit with prophylactic antibiotics used within the first 2 months of induction chemotherapy. The use of high dose gammaglobulin may be required in patients with acute and severe recurrent infections. GM-CSF may be helpful to improve the white blood cell levels in an effort to overcome infectious complications. The use of G or GM-CSF is helpful in the recovery phase following bone marrow or stem cell transplantation.

G and GM-CSF are also used in harvesting stem cells.

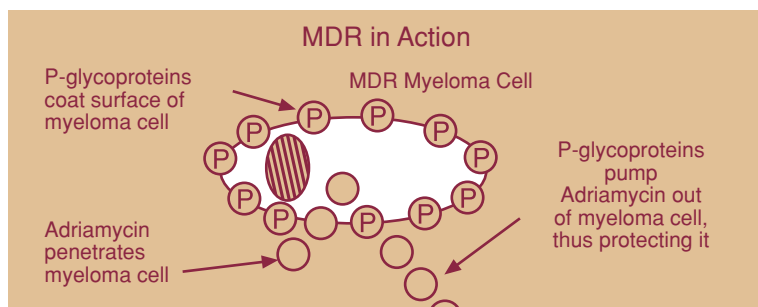
## H. Management of Drug Resistant or Refractory Disease

As illustrated in the pathophysiology section, a frequent problem in myeloma is the relapse which occurs following a 1 to 3 year remission. Although alpha interferon maintenance may be useful in prolonging the initial remission period, the relapse, which supervenes inevitably, requires re-induction chemotherapy. The following is an overall strategy for the management of relapsing disease:

If relapse occurs after a remission of at least six months, the first strategy is to re-utilise the therapy which produced the remission in the first place. Approximately 50% of patients will achieve a second remission with the same therapy that produced the first. This is particularly true for patients in remission for over one year following the initial induction attempt. As an example, a patient who has received MP and has gone into remission for two years can again receive MP induction. If remission has lasted less than six months, some alternative therapy will usually be required. This is also the case if relapse has occurred following a second or third use of the original induction therapy.

The use of VAD is an important consideration in this setting. If VAD is not immediately successful, VAD combined with some new agent, such as PSC 833, to overcome MDR may be appropriate. Please see *Figure 5*:

Figure 5



It is important to keep in mind that a variety of single and combination chemotherapy protocols are available for the management of relapsing and refractory disease. Depending upon the exact problem, a variety of interventions may be possible. For example, if relapse is associated with the development of one or two bone lesions, radiation to the site or sites of bone involvement may be a satisfactory way to manage the relapse. If overall relapse has occurred, the use of dexamethasone as a single agent can be very useful in achieving overall control of the disease. The use of dexamethasone is attractive because it can be given by mouth and does not cause significant side effects such as hair loss or reduction in peripheral blood count values.

Another important point is that relapse following high dose therapy with transplant has, in many cases, a pattern similar to relapse following more standard approaches. Second and sometimes third remissions can be achieved following relapse after bone marrow transplantation. Whether a second high dose therapy with transplant is the most appropriate strategy as opposed to some other lower dose chemotherapy approach is currently unclear. The group at the Royal Marsden Hospital, London, has had excellent results using second and third rounds of high dose melphalan for patients treated in the early to mid 1980's. It is important to note that in this same patient population, the Royal Marsden group has shown clearly that maintenance alpha interferon following high dose therapy does significantly prolong the quality and duration of the remission.

A full range of supportive care aspects are crucial for the management of MM. When first diagnosed, a number of emergency procedures may be required, including dialysis, plasmapheresis, surgery, and radiation to reduce pressure on a nerve, spinal cord, or other crucial organ. The management of pain is essential for the initial care of patients with MM. This can be difficult until initial disease control is achieved. There is no reason for patients with MM to have major ongoing pain with the range of new drugs and strategies available. There can be a reluctance on the part of the patient and/or the physician to implement full pain control procedures because of concerns about addiction. Control of pain should always be the first priority. A brace or corset can help stabilise the spine or other area, reducing movement and pain. Moderate exercise is also important in recovering bone strength and mobility and can help in overall pain reduction.

## I. New Drugs and Strategies

Over the past 5 years there has been a significant increase in new myeloma research projects. New investigators have started to focus on myeloma and several new drugs and strategies have been tested in trials or introduced for general use.

### *Bone Disease*

Since bone damage is the major cause of disability for myeloma patients it is especially encouraging that new drugs are on the horizon. The current bisphosphonates, for example Clodronate and Pamidronate work well but Zoledronate, a new bisphosphonate, is approximately 1000 times more potent in laboratory studies. If the clinical trials now underway go well, a powerful new bisphosphonate may be available for myeloma patients within 2-3 years. Obviously the hope is that it will not only improve bone healing, but further contribute to the slowing of myeloma growth in the bone marrow. Several other drugs are also under development which may be additionally helpful. A new technology called vertebroplasty is also being introduced which may be beneficial for myeloma patients. This procedure involves the injection of plastic cement into a collapsed vertebra in the spine in an effort to recover normal strength and structure for patients disabled by loss of height and spine curvature. Initial results have been encouraging.

### *New Chemotherapy Drugs*

Several new chemotherapy agents have been introduced for the treatment of myeloma. In a recent study from Spain, Navelbine combined with dexamethasone showed considerable promise for patients seeking to achieve remission after failing standard and/or high dose chemotherapy. Likewise, two "Toxoids" (originally derived from the yew tree) called Taxol and Taxotere, as well as a drug which blocks metabolism in drug resistant cells called Topotecan, have shown some activity in relapsing or refractory myeloma. Several trials continue with a drug called PSC 833 which helps reverse drug resistance with the VAD or VAMP protocols. Responses have occurred in patients resistant to VAD and VAMP although the overall impact of such therapy remains to be explored.

### *Biologic Agents*

Since high dose therapy with transplant is still not a curative approach, strategies to delay regrowth of remaining myeloma cells are particularly important. Several new biologic agents have given encouraging results. Perhaps the most exciting is Thalidomide which has shown benefit in reducing myeloma growth and even achieving remissions in patients with relapsing disease. Further studies are required to assess the magnitude and duration of benefit as well as the ideal dosing to reduce side effects. Another strategy is the use of antibiotics to help treat multiple myeloma. Initial studies with Biaxin (Clarithromycin) showed responses in patients with both myeloma and Waldenstrom's. Unfortunately further follow up has indicated that patients need to keep taking the Biaxin to maintain the response. However, dramatic synergism with corticosteroids (e.g. Biaxin + dexamethasone) can be very effective in achieving response in patients refractory to all other modalities including steroids alone. Other new promising biologic agents entering clinical trial are Betathine and interleukins 2 and 12, all of which have shown benefit in pre-clinical and early patient testing.

### *Transplantation*

Numerous studies are under way to improve the outcome with high dose therapy and bone marrow/peripheral stem cell rescue. Strategies include new drugs, different drug dosages (e.g. reducing doses to perform "mini" transplants) and immune cell boosting with infusions of lymphocytes.

### *Vaccines*

Much interest has focused on the potential for boosting natural immunity against myeloma using vaccines. One type using a patient's own cells (dendritic cells) primes the immune system against the exact ("idiotypic") specificity of the myeloma. Another type under development in Southampton, UK, uses DNA combined with an immune stimulator to specifically boost the immune response against myeloma. Time will tell if these can help delay myeloma re-growth.

Strategies are directed against potential causes of myeloma (possible treatment or prevention). Although the cause or causes of myeloma are still not clearly delineated, possible factors include viruses, toxic exposure and stress. "Anti virus" treatment could prove useful in reducing myeloma triggering, as could efforts to reduce stress. Reduction and/or elimination of potential toxic exposures (e.g. pesticides) is obviously a longer term prevention strategy.

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