

The basics

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9 Gayfield Square

Edinburgh

EH1 3NT

Tel: +44 (0) 131 557 3332

Helpline: **0800 980 3332** (UK only)

Fax: +44 (0) 131 556 9720

E-mail: TheIMF@myeloma.org.uk

Website: **www.myeloma.org.uk**

Charity Registration Number: SC 026116

Company Number: 190563

Multiple myeloma

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Introduction

Multiple Myeloma is a relatively rare disease and public awareness is low. Most patients have never heard of Myeloma at the time of diagnosis. The first reactions therefore tend to be a combination of fear of the unknown and confusion about all the new information. A trip to the library is frequently not helpful and may even be misleading. Standard medical information is complex and often out of date or not relevant to the situation at hand.

This handbook is intended to improve that situation; to provide a basic understanding of the disease sufficient to allow patients to make informed decisions about treatment choices. The handbook is supplemental to the information given by the doctor. Caregivers, family and friends may also find the information useful.

Although there is no treatment that can cure Multiple Myeloma, it is an eminently treatable disease. Indeed many patients go on to lead full lives for years even decades after diagnosis. With increasing research the

overall outlook for Myeloma patients is steadily improving. Knowing more about the disease and understanding what can be done to help, reduces anxieties and makes it easier to come to terms with the diagnosis of Myeloma.

Myeloma tends to be a very individual disease. The disease progresses at different speeds and creates a different pattern of problems for each patient. Your doctor will assess your particular situation and recommend the best approach in your case. However, the patient plays a central role in helping make these individual treatment decisions the best they can be. It is important that patients and their families be well informed, ask questions and give serious thought to alternative strategies or options. In this handbook we hope to cover the most important issues to guide management decisions.

What causes Myeloma?

There are over 3000 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 1/100,000 in China to approximately 4/100,000 in most Western industrialised countries. The male/female ratio is 3:2, and 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 towards more frequent Myeloma in patients under age 55, however, implies important environmental causative factors in the past 3 or 4 decades. Exposure to atomic radiation, petroleum products, pesticides, solvents, heavy metals and airborne particles are major risk factors.

What is Myeloma?

Multiple Myeloma is a cancer of plasma cells. Plasma cells are normally present in the bone marrow and are responsible for antibody production in response to infection and other immune triggering events. In Myeloma, a single defective plasma cell (Myeloma cell) gives rise to the much larger number of Myeloma cells which build up in the bone marrow. This process disrupts the normal immune system as well as displacing the normal bone marrow cells. Damage to surrounding bone and soft tissues such as nerves or muscles can also occur. Although the initial growth of Myeloma cells may be in response to a triggering infection (e.g. virus infection) the cells literally take on a life of their own and grow in an uncontrolled or incompletely controlled fashion. The exact mechanisms involved remain to be fully explained. However, the Myeloma cells certainly divide and grow

more frequently than normal plasma cells and develop cancerous properties which enable Myeloma cells to invade and damage bone as well as travel through the blood stream to other bone marrow sites. This latter property is what causes Myeloma to be “multiple” with what are multiple bone marrow (“myelo”) tumours (“omas”). Current evidence indicates that the development of Myeloma is a multistep, multifactorial process. Thus, not only is there uncontrolled growth of the abnormal plasma cells (Myeloma cells) due to DNA damage, but the immune system normally capable of eliminating or blocking cancer development is defective. The dynamic balance of the immune system is therefore shifted in favour of Myeloma cell growth.

The normal bone marrow contains <5% plasma cells. In Multiple Myeloma there are usually >30% plasma cells and this number can increase to over 90% and drastically affect normal bone marrow and immune functions. Thus a bone marrow sample, typically taken from the back of the pelvic bone, shows the increased numbers of plasma cells visible on microscopic examination. Since the bone marrow involvement can be patchy the exact percentage involvement must be interpreted with some caution. In patients with isolated marrow involvement, called solitary plasmacytoma (single tumour site), intervening bone marrow sites, including the standard pelvic

sampling, are normal. Even with more diffuse disease, involving multiple sites, the percentage involvement tends to vary from site to site. The commonest sites of involvement are the pelvis, spine, rib cage, skull plus bones around the shoulders and hips. The amount and activity of the Myeloma in these various sites are the major differences between patients. Whereas one patient can have slowly growing disease in a single site another patient can have aggressive bone destruction at multiple sites plus numerous associated medical complications. Careful initial evaluation, or staging, is therefore crucial as a basis for management decisions.

Bone damage is the most serious concern at the time of initial diagnosis. Myeloma cells produce cytokines such as IL-1, IL-6 and TNF, which are substances which can trigger bone cells, called osteoclasts, to destroy surrounding bone. When more than 30% of the bone has been destroyed, the bone loss is sufficient to show up on x-rays as either thinning (known as osteoporosis) or as dark holes (like Swiss cheese) known as lytic lesions. The weakened area of bone can break. This is called a pathological fracture. This is obviously something to be avoided if at all possible. If a fracture does occur it may require urgent surgical treatment including pinning and/or radiation therapy.

The most common features of Multiple Myeloma at the time of presentation are discussed below.

- 1.** Bone pain is especially common in the middle and/or lower back, rib cage or hips. Pain is mild to severe depending on the size of the lesion, the speed with which it has developed and whether or not a fracture and/or nerve compression have occurred. Typically movement makes the pain much worse.
- 2.** Fatigue is also common and is usually proportional to the severity of anaemia. Obviously, in addition, the overall impact of the disease can worsen fatigue.
- 3.** Symptoms of infection depend upon the site of infection. Pneumonia, bladder or kidney infection, sinusitis and skin infections are particularly common. The reduced immunity in patients with active Myeloma predisposes to infection.
- 4.** Symptoms due to hypercalcaemia (increased blood calcium). Blood calcium levels increase due to a combination of calcium release into the blood stream from destroyed bone and reduced calcium excretion due to kidney damage. Symptoms such as thirst, nausea, constipation and mental confusion occur and can steadily worsen until blood calcium levels are brought under control.

Initial Diagnosis

Prior to the widespread use of blood and urine testing for screening purposes, some or all of the aforementioned symptoms usually lead to the diagnosis. Nowadays, abnormalities picked up on routine blood screening and/or urine tests, may lead to diagnosis even before major symptoms have emerged. There is therefore the opportunity to prevent or avoid major bone or kidney damage and other associated problems.

Investigations to confirm a diagnosis

As for other types of cancer, a biopsy showing the malignant cells is the cornerstone of the diagnosis. The diagnosis of Myeloma is confirmed by:

1. A bone marrow sample containing at least 10% but usually >30% plasma cells. The malignant nature of the Myeloma cells is confirmed by the monoclonal pattern (i.e. all kappa or all lambda light chain subtyping of

the Myeloma cells), abnormal chromosomes and/or the typical malignant appearance under the microscope when examined by an experienced haematopathologist.

2. Direct biopsy from a plasmacytoma. Myeloma can present as a single or multiple tumours in bone or soft tissue. Direct biopsy usually shows 90-100% Myeloma cells in the tumour confirming the diagnosis of a solitary plasmacytoma or Multiple Myeloma.

3. Supportive findings. If there is no direct biopsy and the bone marrow contains <30% plasma cells, a definitive diagnosis of Myeloma requires either:

(I) A high level of Myeloma protein (M-component or monoclonal protein) in the blood and/or urine. See “staging” section page 12.

or

(II) Definitive evidence of Myeloma on x-ray. A bone or “full skeletal” survey is required to assess for lytic lesions and/or significant osteoporosis. If there is osteoporosis only, other evidence of bone and/or bone marrow involvement is required. This usually leads to MRI and/or other scanning such as FDG/PET scanning or MIBI scanning.

Borderline cases may require further testing and/or serial monitoring to distinguish between Monoclonal Gammopathy of Undetermined Significance (MGUS) or smouldering Myeloma both of which require no treatment (see below).

What's NOT Myeloma?

Sometimes initial testing can suggest a possible diagnosis of Myeloma which is not confirmed by additional testing or monitoring. Occasionally a monoclonal protein develops in response to some other underlying illness such as an "auto immune" disease (e.g. systemic lupus erythematosus, scleroderma), neurological disease (e.g. multiple sclerosis, amyotrophic lateral sclerosis [ALS]) or a long standing infectious process (e.g. tuberculosis). However, what is not Myeloma is usually one of the three conditions listed below:

1. Solitary plasmacytoma. As already mentioned, the growth of Myeloma can start in a single site, most commonly the spine or pelvis. Occasionally the site can occur outside bone in soft tissue. The most common place for a soft tissue plasmacytoma is in the head and neck region. Patients with a solitary plasmacytoma can have a monoclonal (i.e. Myeloma) protein in the blood and/or urine. If a solitary plasmacytoma is removed by surgery

and/or eradicated with radiotherapy, over a few weeks the Myeloma protein will completely disappear. This disappearance confirms the diagnosis and argues against Multiple Myeloma. Unfortunately, this does not rule out the possibility of reoccurrence elsewhere, but typically a remission period measured in years rather than months can be expected following successful treatment of a solitary lesion.

2. Monoclonal Gammopathy of Undetermined Significance (MGUS). This is a condition in which the level of plasma cell involvement is low (usually <10% or certainly < 20%) and no growth is occurring (growth or labelling index of plasma cells = 0%). There is no bone damage, blood counts tend to be completely normal and the patient frequently has no symptoms. In this instance no treatment is required. However, careful ongoing monitoring is required. If the disease is stable for two years it may remain stable for many years. Still there is a percentage risk (approximately 30%), that Myeloma may have developed by the ten year time point. Obviously it is crucial to diagnose MGUS and avoid unnecessary treatment.

3. Indolent Myeloma. This is a condition somewhere between MGUS and full blown Myeloma. In this instance there is evidence of bone damage and possible blood count as well as other problems, but very slow progression means that minimal or no treatment may be required over long periods.

A related condition is “Smouldering Myeloma” in which there are no bone lesions, but the Myeloma protein and bone marrow plasma cell levels are higher than in traditional MGUS. Stable or slowly changing disease is common in this setting also.

Staging and Prognostic Factors

When a diagnosis is made it is important to evaluate two aspects:

1. How much Myeloma is there?

The traditional method of assessing the amount of Myeloma is using the Durie-Salmon staging system. This allows classification of patients into stage I (early disease) to stage III (late disease) and A (normal kidney function) or B (abnormal kidney function).

For example:

Stage I A – low amount of Myeloma – normal kidney function
Stage III B – high amount of Myeloma – abnormal kidney function

The staging system is based upon the number of bone lesions, severity of the anaemia due to bone marrow replacement with Myeloma, level of protein in the blood and/or urine and serum calcium level.

Typically patients with stage III disease will require more urgent treatment especially stage III B when immediate intervention may be required to protect and/or recover kidney function.

2. How aggressive is the Myeloma?

As mentioned earlier, the speed of progression of the Myeloma varies from patient to patient. This ranges from progression occurring in a few weeks to several years. The tendency for change is reflected in different tests. For example, growth rate is reflected by the labelling index which gives the number and percentage of Myeloma cells which are actively growing and dividing. The serum B2 microglobulin blood test indicates both the amount and the activity of the Myeloma. Bone marrow chromosome testing indicates if any Myeloma chromosome damage is present. As one might expect, the more chromosome damage there is, especially certain chromosomes such as numbers 11, 13 and 14, the less likely it is that the standard approaches to treatment will work well. Problems with chromosomes numbers 5 and 7 suggest damage to the normal bone marrow stem cells or myelodysplastic syndrome (M.D.S.).

There are many tests which can be used if necessary to assess the pattern of disease including tendency for bone damage and/or deposition of Myeloma protein in tissues and organs in the form of amyloid deposits.

The standard typing of Myeloma by heavy and light chain is also helpful.

The most common types of Myeloma are:

IgG: k or lambda

IgA: k or lambda

K or lambda only (Bence Jones Myeloma)

Rarer types are:

IgD: k or lambda

IgM: k or lambda

IgE: k or lambda

These types have some prognostic implications. For example, the lambda subtype is more commonly associated with amyloid deposits especially in the nerves or the kidneys. Patients with IgG kappa Myeloma tend to have the overall best survival.

Treatment

1. Direct approaches to eradicate the Myeloma Cells

A. Chemotherapy

Chemotherapy destroys the malignant plasma cells (Myeloma cells), with the aim of inducing remission or cure. It involves administering anti-cancer drugs via injection or by mouth (orally). Chemotherapy regimens (treatment programmes) generally stretch over a period of months. Most often, they are administered on an out patient basis.

The drugs are administered in cycles giving the patient's immune system and normal bone marrow cells, which are weakened by the chemotherapy, time to recover between cycles. By killing malignant cells, chemotherapy can also relieve many of the symptoms of the disease including anaemia, hypercalcaemia, bone destruction and abnormal blood/urine protein levels.

Chemotherapy is said to be effective if it reduces the abnormal blood/urine protein levels and/or the percentage of Myeloma cells observed in the bone marrow. It may be considered successful even if it does not induce full remission (return to normal levels). There are many chemotherapy options involving different combinations and dosages of drugs which are administered using different protocols (schedules for treatments, diagnostic tests and decisions on future treatment).

Side Effects of Chemotherapy

General side effects of chemotherapy include: hair loss, nausea and vomiting, increased risk of bruising, bleeding and infection, mouth sores and ulcers. With some chemotherapy agents abdominal cramps, constipation, numbness and tingling in the hands or feet may be experienced. Fertility may also be affected.

Not everyone will experience all the side effects, this will depend on a number of factors, such as the dose given and the person's general health.

B. Radiation Therapy

This is typically used in a localised area where there is bone destruction and pain. Radiation is also used in an effort to completely eradicate Myeloma cells from an area in which a plasmacytoma has been surgically removed. The affected area is exposed to controlled doses of radiation. Radiation can kill malignant cells more quickly than chemotherapy and has fewer side effects. It is therefore used to achieve quicker pain relief, control severe bone destruction and for patients not able to tolerate chemotherapy regimens. It can also be used in conjunction with chemotherapy. Radiation therapy is generally given five times a week over a period of weeks or

months. Treatment can normally be on an out patient basis. Decisions to be made by the radiation therapist with regard to radiation therapy include the dosage, the area to be treated and the period over which the treatment is given.

C. Bone Marrow Transplant (BMT) and Peripheral Blood Stem Cell Transplant (PBSCT)

Transplants are being evaluated in clinical trials as alternatives to conventional treatment and as potential cures for Myeloma. However, no type of transplant is yet definitely curative for Myeloma. Typically transplantation involves extremely high dose chemotherapy, sometimes combined with whole body radiation therapy. The therapy is so potent that it destroys all of the patient's bone marrow. Without the bone marrow, there is no immune system and no ability to manufacture new blood cells, and the patient cannot live. The marrow transplant procedure replaces the destroyed marrow, rescuing the patient. Thus, the marrow transplant procedure is a means of administering treatment doses that would otherwise prove fatal. It is hoped that by destroying the marrow, all of the malignant Myeloma cells will also be destroyed. The transplanted marrow is drawn from a genetically matched donor (allogeneic transplant) or the patient (autologous transplant). When the patient's own marrow is used,

it can be purged using chemicals or antibodies designed to remove malignant cells before it is transplanted. Bone marrow and stem cell transplants require preparatory chemotherapy regimens (e.g. VAD chemotherapy) most often administered over a period of months. The transplant itself might involve a hospital stay (weeks to months) followed by a period of reduced activity. Transplants are by far the most aggressive treatment programmes in use today and they also have the highest level of risk. Decisions to be made by the treating physician with regard to bone marrow and/or stem cell transplants include allogeneic (using a sibling's or compatible donor's marrow) vs. autologous (using the patient's own marrow), preparatory chemotherapy and radiation therapies and anti-rejection measures. For autologous transplants, decisions must also be made on marrow purging techniques. Transplants remain the subject of much controversy as researchers strive to learn their impact on overall survival, their proper timing and overall role in the treatment of Myeloma.

D. Maintenance Therapy

After remission is achieved, maintenance therapy is used to help prolong or maintain remission. Maintenance is used after both conventional chemotherapy and high dose chemotherapy plus transplant.

Many types of treatment have been tested in this setting, however only a few have shown benefit:

(I) Alpha Interferon: Numerous studies have shown that alpha interferon can prolong remission especially if an excellent remission is achieved with chemotherapy or transplant. Unfortunately it only delays, but does not prevent relapse. Side effects of fatigue and low grade fever, along with the need for injections three times per week limit the usefulness of interferon.

(II) Steroids (prednisone or prednisolone): Steroids, such as prednisone tablets, taken by mouth can be used to prolong remission. Recent studies have shown that prednisone taken either 3 times a week or on an every other day basis can both prolong remission and overall survival. Although steroids also have side effects, in general these can be minimised by changes in dose and/or schedule.

(III) Supportive care measures: A variety of supportive care measures can be helpful for maintenance including the use of bisphosphonates (e.g. clodronate, pamidronate) which not only help bone disease, but may also prolong remission. Erythropoietin by injection improves both haemoglobin and the general quality of remission.

(IV) New approaches: The search for better maintenance treatment is a top priority for many Myeloma specialist. New protocols testing vaccines or new drugs may be suggested in an effort achieve better results.

2. Treatment directed at relieving symptoms:

Includes administering drugs to control hypercalcaemia, bone destruction (resorption), pain and infection.

(I) Pain: Most people with Myeloma will experience bone pain at some time. Surgery may be used to shrink/eliminate tumours or repair bone damage and/or reduce pain. A whole range of pain medications and procedures (e.g. local anaesthetic) are available to relieve pain. With currently available pain strategies no patient should suffer needlessly. Many centres now have specialised pain management teams.

(II) Infection: Antibiotics and vaccines can play a role in preventing and combating opportunistic infections.

(III) Anaemia: Erythropoietin can be administered to relieve anaemia and the symptoms that accompany it e.g. fatigue.

(IV) Hypercalcaemia: Bisphosphonates can significantly reduce bone damage and therefore provide relief for hypercalcaemia in Myeloma.

(V) Other Medications: Other medications and supplements should be taken with care when under treatment for Myeloma. Ideally no additional medications or supplements should be taken without the advice of a physician who is fully familiar with the patient's medical status and treatment programme. For example, seemingly innocent over-the-counter anti-inflammatory medications can cause kidney damage in some Myeloma patients with already reduced kidney function.

What results should one expect from treatment?

1. Stabilising- Countering the life threatening disruptions to body chemistry and the immune system that can occur with Myeloma.
2. Palliative- Relieving discomfort and increasing the patient's ability to function normally.
3. Remission- Lessening the severity of the symptoms, slowing or temporarily arresting the course of the disease.

4. Cure- achieving a permanent remission (this has rarely, if ever, been achieved and confirmed).

To say it another way, treatment is given to make the patient feel better and function better. It may also control the effects of the disease on normal body function, slow the disease down or halt it temporarily. Remissions can last from months to decades. Experimental treatments aim at a cure, although none has yet been confirmed.

How should one choose among available treatments?

Treatment recommendations are received when the patient is first diagnosed or upon discovery of a relapse. Understandably the patient is upset and often not well informed about the disease or the treatment options. The situation is generally charged with emotion and does not lend itself to complex, technical explanation and careful contemplation of alternatives. Most doctors recognise this and focus on getting the patient to accept the more critical next steps, leaving the less critical decisions for a less emotional moment.

If you need to make a treatment decision, the first rule is to stop and think.

Other than crisis intervention to deal with acute life-threatening symptoms, there are few decisions that cannot wait long enough for a second opinion or personal reflection. Also, certain treatment decisions can rule out future options. For example, certain types of chemotherapy should not be used if an autologous bone marrow transplant is likely in the future.

This is NOT to suggest that patients refuse critical treatment.

However, it is important to ask your doctor which treatment decisions are critical and which can wait. When the situation permits, take the time to get more than one opinion before beginning a treatment programme.

When talking about treatments, start by understanding the objectives. Treatment recommendations typically include multiple components, each with different objectives. Often, certain elements of the treatment programme are more urgent than others and require quicker decisions. Others aim more at long-term management of the disease, allowing more time to decide.

Beyond some tried and true stabilising and palliative treatments there are very few absolutes in Myeloma treatment. For example bone marrow or stem cell transplantation is not an absolute requirement even when feasible in a young and otherwise healthy patient. Remission inducing treatments,

typically chemotherapy programmes, cannot guarantee results. Doctors have information on success rates and can use different tests to help choose the programmes that have the best odds. The same can also be said of bone marrow transplants, which aim at cure.

Conclusion

To make an informed decision the patient needs to have all the facts. Much of what is written about Myeloma is written by doctors and researchers to be read by other doctors and researchers. As a result, the literature tends to be very difficult to read for the patient and other concerned lay persons.

As such, the doctor(s) treating the patient bear the burden of education. Yet, doctors must take their cues from the patient and family on how far to go on this front. Some patients are fiercely curious and want to discuss all aspects of their situation, treatment and prognosis. Others are overwhelmed and just want to know what to do next.

Most doctors are sensitive to this and will vary their approach based on what they perceive to be the patient's wishes. Patients can shortcut the process by being very explicit about how deeply they want to get into the details of the treatment decision.

Treatment decisions are critically important to the survival and quality of life of the Myeloma patient. No matter how comfortable the patient feels with a doctor, it is generally good practice to get more than one opinion before proceeding.

Because the disease is rare, there are a limited number of practitioners and research/treatment centres specialising in Myeloma. Doctors understand this and will be helpful in identifying appropriate specialists and making referrals. It is very common to seek a second opinion from a specialist at a research centre and to continue to rely on your local referring physician to administer and monitor treatment.

Making good decisions on Myeloma treatment requires resourcefulness, careful questioning, serious thought, and courage. Most of all, it requires that the patient and his/her support group take charge of the process.

Self-help

What can I do to help myself?

Start by asking questions, here are a few examples:

1. Treatment programme

Get a complete description:

What are the objectives of the treatment?

What exactly is the treatment?

Over what period will it be given?

What is involved?

How often must a patient visit a medical facility?

Is hospitalisation required or a possibility?

What is the likely impact on the patient's ability to function e.g. work and play?

How do people feel before, during and after treatment?

How long will they be undergoing treatment?

What are typical recovery time frames?

What follow-up or maintenance programmes are required?

2. Past experience

Find out how well the treatment has worked for others in similar situations. Effectiveness is usually measured in many different ways. The questions to ask here are:

How much experience is there with the treatment?

How many patients have received the treatment?

How long have those been followed after their treatment?

What are the chances of achieving a complete or partial remission?

How long have other patient's remissions lasted?

In the event of a relapse, what would the options be, recognising that these may change in the interim?

What are reasonable expectations for relieving symptoms such as bone pain, pathological fractures, anaemia, fatigue and hypercalcaemia?

What factors are seen as an influence to outcomes?

How long have people who have received the treatment survived?

For newer treatments:

How many of the original group of patients are still alive?

3. Find out about side-effects

Like most cancer treatments, Myeloma treatments generally use strong drugs and other measures aimed at destroying malignant cells and/or re-balancing body chemistry. Typically, there are side effects. Some manifest themselves during treatment. Others may show up well after the treatment. Questions to ask here are:

- What side-effects have been observed in patients receiving the treatment?
- When do they typically occur?
- How often do they occur i.e. what percentage of patients are affected?
- How serious are these effects, are they life threatening, are they painful, are they permanent, how long do they last?
- Are there treatments for the side effects, do they have side effects?

4. Find out about alternatives

Perhaps, the most important line of questioning is about alternatives. There are always alternatives. You need to ask all of these questions for each of the alternatives:

- What are the alternatives to the treatment recommended?
- What are the relative pros and cons of the alternatives?
- What are the pros and cons of the alternative treatments versus no treatment?

The Future

The outlook for a person with Multiple Myeloma is continually improving. Researchers continue to look for better ways to diagnose and treat Myeloma, their knowledge about the disease is growing all the time. Many of these exciting research projects are being supported by the International Myeloma Foundation all over the world.

International Myeloma Foundation (UK)

IMF(UK) are dedicated to improving the quality of life of Myeloma patients while working towards prevention and a cure. The foundation provides a number of support, informational and educational services to Myeloma patients, their families/carers and health care professionals as well as raising money to fund important research. These important services are overseen by a Management Board which is guided by expert Scientific and Patient Advisory Boards.

We encourage you to make use of the services the Foundation provides and hope you will contact us in the future for more information.

International Myeloma Foundation (UK)
9 Gayfield Square
Edinburgh Scotland
EH1 3NT
Tel: +44 (0) 131 557 3332
Helpline: **0800 980 3332** (UK only)
Fax: +44 (0) 131 556 9720
E-Mail: The IMF@myeloma.org.uk
Website: www.myeloma.org.uk

Other useful organisations

International Myeloma Foundation

International Headquarters
12650 Riverside Drive, Suite 206
North Hollywood
CA 91607-3421
USA
Tel: +1 818 487 7455
Fax: +1 818 487 7454
www.myeloma.org

CancerBACUP

3 Bath Place
Rivington Street
London EC2A 3DR
Tel: 020 7696 9003
Fax: 020 7696 9002

Cancer Information Freephone:
0808 800 1234
www.cancerbacup.org.uk

Cancerlink

11-21 Northdown Street
London N1 9BN
Tel: 020 7833 2818
Fax: 020 7833 4963

Freephone Support Link:
0808 808 0000
www.cancerlink.org

Irish Cancer Society

5 Northumberland Road
Dublin 4
Ireland
Tel: + 353 (0) 1 668 1855
Fax: + 353 (0) 1 668 7599
www.cancer.ie

Leukaemia Research Fund

43 Great Ormond Street
London WC1N 3JJ
Tel: 020 7405 0101
Fax: 020 7242 1488
www.lrf.org.uk

The Ulster Cancer Foundation

40/42 Eglantine Avenue
Belfast BT9 6DX
Northern Ireland
Tel: 028 9066 3281
Fax: 028 9066 0081
www.ulstercancer.org

Terms and Definitions

Alkylating Agent: A chemotherapeutic agent such as melphalan or cyclophosphamide. Alkylating refers to the way in which these agents cross-link the DNA of Myeloma cells and block cell division.

Amyloidosis: A condition in which Myeloma light chains (Bence Jones proteins) are deposited in tissues and organs throughout the body. This occurs more commonly with lambda versus kappa Bence Jones proteins. In patients with amyloidosis the light chain proteins bind to certain tissues such as heart, nerves and kidney rather than being excreted out of the body through the kidneys.

Anaemia: A decrease in the normal number of red blood cells, usually below 10 G% with over 13-14 G% being normal. Myeloma in the bone marrow blocks red cell production causing anaemia (shortness of breath, weakness and tiredness).

Antibodies: Proteins produced by white blood cells to fight infection and disease.

Appendicular Skeleton: The long bones (i.e. arms and legs) which are attached to spine, chest and pelvis.

Axial Skeleton: The skull, spine and pelvis region of the skeleton.

Bence Jones: The name used to identify Myeloma protein present in urine.

The Myeloma or M protein: Consists of kappa or lambda light chains. The amount of Bence Jones protein is expressed in terms of G per 24 hours. Normally a very small amount of protein (less than 0.1 G per 24 hours) can be present in the urine, but this is albumin rather than Bence Jones protein. The presence of any Bence Jones protein is abnormal.

Beta 2 Microglobulin: A small protein found in the blood. High levels occur in patients with active Myeloma. Low or normal levels occur in patients with early Myeloma and/or inactive disease. Approximately 10% of patients have Myeloma which does not produce beta 2 microglobulin. For these patients, beta 2 microglobulin testing cannot be used to monitor the disease. At the time of relapse, beta 2 microglobulin can increase before there is any change in the Myeloma protein level. Therefore, 90% of the time, beta 2 microglobulin is very useful for determining disease activity.

Bisphosphonate: A type of drug which binds to the surface of bone where it is being resorbed (eaten into) and protects against osteoclast activity.

Bone Marrow: The soft, spongy tissue found in the centre of bones.

Bone Marrow Aspiration: The removal, by needle, of fluid and cells from the bone marrow.

Bone Marrow Biopsy: The removal, by needle, of a sample of tissue from the bone marrow.

Bone Remodelling: The co-ordinated, or coupled, activity of osteoclasts (which resorb or destroy bone) and osteoblasts (which create new bone matrix) to form new bone while destroying old bone in a balanced way such that the total amount of bone remains the same.

Calcitonin: A hormone secreted by the thyroid gland which blocks bone resorption temporarily.

Calcitriol: An activated form of Vitamin D useful for persons who require extra vitamin D.

Calcium: The mineral which makes up the hard stuff of bone matrix or hydroxyapatite.

CAT (Computerised Axial Tomography) Scan: A computerised x-ray study used to detect small areas of bone damage or soft tissue involvement.

Chemotherapy: Treatment with anti-cancer drugs.

Clinical Trials: Studies of new treatments.

Consolidation Therapy: A phase of treatment in which an effort is made to improve the response achieved with the initial approach to treatment. Consolidation typically involves either higher dosages or drugs not previously used.

Coupling: The normal co-ordination between osteoblasts and osteoclasts to maintain a balanced state of bone production and destruction.

Creatinine: A small chemical compound normally excreted by kidney. If the kidneys are damaged the serum level of creatinine builds up resulting in an elevated serum creatinine. The serum creatinine test is used to measure kidney function.

Cytokine: A substance that stimulates growth/activity in a particular type of cell. Cytokines are produced locally (i.e. in the bone marrow) as well as circulating in the blood stream.

DEXA (Dual Photon X-ray Absorptionmetry): An x-ray study which can measure the amount of bone loss; the best measure of bone density.

Dexamethasone: A steroid given along with other chemotherapy drugs.

Dialysis: When a patient's kidneys are unable to filter blood, the blood is cleaned by passing it through a dialysis machine.

Electrophoresis: A laboratory test in which a patient's serum is subjected to a separation technique involving movement in an electric field. The amount of movement is determined by the size and the electric charge of the protein involved. The technique allows both the calculation of the amount of Myeloma protein as well as the identification of the specific M spike characteristic for each patient. Used as a tool both for diagnosis and monitoring.

Erythropoietin: Erythropoietin is a hormone produced by the kidneys. Myeloma patients with damaged kidneys don't produce enough erythropoietin and can become anaemic. Injections with synthetic erythropoietin can be helpful. Blood transfusion is another alternative, especially in an emergency. Synthetic erythropoietin is being used prophylactically before chemotherapy and as a supportive therapy after chemotherapy to avoid anaemia.

Hypercalcaemia: Elevation in the blood calcium level. Common in Myeloma patients and usually resulting from bone destruction with release of calcium into the blood stream. It is often associated with reduced kidney function since calcium can be toxic to the

kidneys. For this reason, hypercalcaemia is usually treated on an emergency basis using IV fluids combined with drugs to reduce bone destruction along with direct treatment for the Myeloma.

IgG, IgA: The two most common types of Multiple Myeloma. The G and the A refer to the type of protein produced by the Myeloma cells. The Myeloma protein, which is an immunoglobulin, consists of two heavy chains, for example of a G type combined with two light chains which are either kappa or lambda. Therefore the two most common subtypes of Myeloma have identical heavy chains (i.e. IgG kappa and IgG lambda). The kappa and lambda light chains can be produced alone resulting in either kappa or lambda light chain (Bence Jones) Myeloma. The terms heavy and light refer to the size or molecular weight of the protein with the heavy chains being larger than the light chains. Since the light chains are smaller, they are more likely to leak out into the urine resulting in urine Bence Jones protein.

IgD, IgE: Two types of Myeloma, similar to IgG and IgA, which occur less frequently.

Immunofixation: Immunologic method used to identify M-protein type (IgG, IgA, kappa or lambda). The most sensitive routine immunostaining technique, it identifies the exact heavy and light chain type of the M-protein.

Induction Therapy: The initial treatment used in an effort to achieve remission in a newly diagnosed Myeloma patient.

Interferon: A cytokine (or hormone) which produced normally in response to virus infection. Produced by genetic engineering techniques, synthetic interferon is given as treatment for Myeloma and is used primarily in the maintenance (or plateau) phase to block any re-growth of Myeloma and thus delays or prevents relapse.

Interleukin-6: A cytokine which is a potent stimulus to osteoclast and plasma cell activities.

Lytic Lesion: The damaged area of a bone that shows up as a dark spot on an x-ray when enough of the healthy bone in any one area is eaten away. Lytic lesions look like holes in the bone and are evidence that the bone is being weakened.

Monoclonal: Myeloma develops from a single malignant plasma cell (monoclonal). The type of Myeloma protein produced is also monoclonal; a single form rather than many forms (polyclonal). The important practical aspect of a monoclonal protein is that it shows up as a sharp spike (M spike) in the serum electrophoresis test.

M-protein: An antibody produced by the Myeloma cell and found in the blood or urine; synonymous with monoclonal protein, Myeloma protein and M spike.

MRI (Magnetic Resonance Imaging): Magnetic energy rather than x-ray energy, used to obtain an image of the body gives very fine resolution of soft tissues, especially encroachments on the spinal cord, but is less accurate for bone lesions.

M spike: Another name for M protein. Spike refers to the sharp or spiked pattern which occurs on protein electrophoresis when an M protein is present.

Multi Drug Resistance (MDR): A resistance to standard treatment, it is typically associated with resistance to adriamycin and vincristine, both chemotherapy drugs. The resistance is caused by a build up of the p-glyco protein in the outer cell membrane of the Myeloma cells. This results in drugs, such a adriamycin, being kicked back out of the Myeloma cell instead

of building up in the Myeloma cell and eventually killing that cell. Drugs which block this p-glyco protein pump are now in clinical trials (e.g. PSC833, a new cyclosporin analogue).

Nephelometry: A readily available and rapid automated laboratory method to determine the amount of Myeloma protein in the blood (see "immunofixation" which identifies the type of Myeloma protein). Nephelometry uses a light scattering technique and should be checked against electrophoresis to ensure accuracy.

Neutropenia: A reduced level of neutrophils or white blood cells. There are several types of white blood cells, and neutropenia refers to a reduction in the granulocytes, or neutrophils, necessary to adequately combat bacterial infections. Cytotoxic chemotherapy has a tendency to induce neutropenia. In contrast, lymphocytes which are more important in virus infections, tend not to be affected by cytotoxic treatment.

Osteoblast: The cell which produces osteoid which becomes mineralised with calcium to form new hard bone.

Osteoclast: A cell found in the bone marrow at the junction between the bone marrow and the bone. Active Myeloma growth stimulates the osteoclast to destroy bone. This process

is called resorption. Normally bone resorption is counter balanced by the activity of osteoblasts which create new bone. In Myeloma, osteoblast activity is blocked. The combination of accelerated bone resorption and blocked new bone formation results in lytic lesions.

Osteoid: The protein product which becomes mineralised with calcium to form hard bones.

Osteoporosis: Reduction in bone density typically associated with old age. Diffuse involvement of bones with Myeloma produces what looks like osteoporosis on x-ray and bone density measurement.

Pathological Fractures: Occurs in Myeloma-weakened bones which can't bear the normal weight or stress.

Plasma Cell: The malignant cell in Myeloma. Normal plasma cells produce antibodies to fight infection. In Myeloma, the malignant plasma cells produce large amounts of abnormal antibodies which lack the capability to fight infection. The abnormal antibodies are the monoclonal protein, or M protein. Plasma cells also produce other chemicals which can result in organ and tissue damage (i.e. anaemia, kidney damage and nerve damage).

Plasmacytoma: A collection of plasma cells found in a single location rather than diffusely throughout the bone marrow, soft tissue or bone.

Plasmapheresis: The removal of certain proteins from the blood.

Platelet: One of the three major blood cells, others being the red and white cells. Platelets plug up breaks in the blood vessel walls and stimulate blood clot formation. Platelets are the major defence against bleeding.

Progression-Free Survival: The improved survival of a patient that can be directly attributed to the treatment given for the Myeloma. This term identifies Myeloma patients who are in complete remission versus those who have had an episode of relapse (or progression).

Radiation Therapy: Treatment with high energy rays to kill malignant cells.

Red Cells: The blood cell which contains haemoglobin and carries oxygen from the lungs to all parts of the body. A low level of red cells is called anaemia. Red cell production is stimulated by a hormone called erythropoietin. Erythropoietin is produced by the kidneys. Myeloma patients with damaged kidneys don't produce enough erythropoietin and can become anaemic. Injections with

synthetic erythropoietin can be helpful. Blood transfusion is another alternative, especially in an emergency. Synthetic erythropoietin is being used prophylactically before chemotherapy and as supportive therapy after chemotherapy to avoid anaemia.

Response or Remission: – Complete Remission or Complete Response (CR): Remission and response are used interchangeably. CR is the common abbreviation for both. CR is the absence of Myeloma protein from the serum and/or urine by standard testing; absence of Myeloma cells from the bone marrow and/or other areas of Myeloma involvement; clinical remission and improvement of other laboratory parameters to normal. The absence of Myeloma cells and Myeloma protein does not mean that the Myeloma has gone. Sensitive testing methods can detect minute levels of Myeloma. Relapse occurs after complete and partial remission. The time to relapse is influenced by the type of initial treatment as well as the maintenance used.

– Partial Remission or Partial Response (PR): PR is a level of response less than CR. In SWOG studies, it has meant >50%<75% response. In other studies it has meant >50% response.

Stable Disease: This describes patients who have some response to treatment, but <50% reduction in Myeloma protein levels. Stable disease is not necessarily bad or sub-optimal (as compared to CR or PR) provided the Myeloma has stabilised and is not progressing. An acceptable remission (i.e. number of months/years in remission) is not necessarily proportional to the percentage response. With slow moving Myeloma, stabilisation can last for many years.

Serum Osteocalcin: A protein produced and secreted by osteoblasts when they are making osteoid. A low level reflects active Myeloma. A higher than normal level reflects more stable Myeloma.

Skeletal Survey/Metastatic Survey: A series of plain x-rays of the skull, spine, ribs, pelvis and long bones to look for lytic lesions and/or osteoporosis.

Stem Cell: Normal stem cells give rise to normal blood components, including red cells, white cells and platelets. Stem cells are normally located in the bone marrow and can be harvested for transplant.

Thrombocytopenia: A reduced level of blood platelets. The normal level is 150-250 000. Bleeding problems occur when the platelet level is less than 50 000. Major bleeding is

usually associated with a reduction to less than 10,000.

Transplantation: Stem cells or bone marrow are used to rescue to patient's blood-forming potential following very high dose chemotherapy and/or radiation treatment. Transplant is not a treatment, but a method of support to make high dose treatment possible.

– Allogeneic: The person donating the bone marrow or stem cells is an HLA identical family member. HLA refers to the Histo-compatibility Locus Antigens used for tissue matching (Unrelated Allogeneic Transplant = the person donating is unrelated to the patient).

– Autologous : The patient donates his/her own stem cells or bone marrow, prior to treatment, for re-infusion later.

– Peripheral Blood Stem Cells (PBSC): Stem cells are collected from the circulating blood system, not from the bone marrow.

– Syngenic: An identical twin donates the bone marrow or stem cells.

White Cells: One of the three major types of cells in the blood. There are several types of white cells (i.e. neutrophils, lymphocytes and monocytes). Neutrophils are necessary to combat bacterial infection. Neutrophils can drop to very low levels following

chemotherapy causing neutropenia. Neutropenia can be prevented or reduced using a synthetic hormone called G-CSF (e.g. Neupogen).

Common tests used to evaluate Myeloma

Amyloidosis: Subcutaneous fat biopsy. If negative, Congo red staining of bone marrow, kidney or rectal biopsy can be carried out.

Blood: Routine blood counts, renal and liver function tests, chemistry panel tests, LDH, Myeloma protein level, serum beta 2 microglobulin, CRP and peripheral blood labelling index.

Bone Marrow: Used to make the diagnosis and to monitor the disease status.

Bones: Routine skeletal survey (x-ray), MRI and/or CT scanning for questionable areas. More experimental tests are whole body MIBI and/or PET scanning.

Urine: 24 hour collection for measurement of Bence Jones protein and creatinine clearance.