Understanding and managing myeloma

In this article...
- Who is at risk of developing myeloma
- How myeloma is diagnosed
- Treatment regimens and ways to manage the disease

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Multiple myeloma cannot be cured and treatment can be complex. This article outlines the pathophysiology of the condition, together with the diagnostic process and the available treatment options.

Myeloma (also known as multiple myeloma or myelomatosis) is a blood cancer characterised by the proliferation and accumulation of abnormal plasma cells in the bone marrow and, in almost all cases, the presence of an abnormal molecule called a paraprotein (also known as an M protein or spike). It is thought to be preceded in all cases by a pre-malignant condition called monoclonal gammopathy of undetermined significance (MGUS) (Dhodapkar et al, 2014).

Early stages of myeloma may be asymptomatic; this is called “smouldering myeloma”. There are specific criteria for differentiating between MGUS, smouldering myeloma and symptomatic (clinical) myeloma (Table 1). Although MGUS is often monitored in primary care (Bird et al, 2009; Rawstron et al, 2007), there is increasing evidence that it may not be benign in all cases (Van De Donk et al, 2014) and collaboration with a haematologist is advisable.

During progression from MGUS to symptomatic myeloma, the abnormal plasma cells acquire increasing numbers of genetic abnormalities. A patient’s myeloma cells will consist of multiple populations of cells with distinct patterns of genetic abnormalities. These populations compete with each other and it is thought that this may play a part in relapse and the evolution of drug resistance (Walker et al, 2014).

The key features defining symptomatic myeloma are the presence of:
- Large numbers of clonal plasma cells in bone marrow;
- Serum M protein;
- Raised calcium levels, renal abnormalities, anaemia or bone damage – referred to as CRAB (Talamo et al, 2010).

Myeloma has been described as “a cancer with highly protean behaviour” (Talamo et al, 2010), meaning it presents in many different ways. It is often diagnosed on renal or orthopaedic wards, and may present in an emergency setting, for example, after spinal cord compression. This means it is wise to consider that unexplained signs or symptoms may be caused by myeloma. This is particularly true in older patients but it is important not to dismiss the possibility of myeloma in younger adults. Diagnosis may be delayed by “diagnostic tunnel vision” but, if diagnosed and treated early, young adults have a very good prognosis.

The presence of large numbers of plasma cells in the circulating blood is rare and usually indicates late-stage disease. This is called secondary plasma-cell leukaemia and is associated with a poor prognosis (Fernandez De Larrea et al, 2013). If plasma cells are present in the blood and marrow but there are no localised bone lesions at diagnosis, the condition is classified as plasma-cell leukaemia (Albarracin and Fonseca, 2011). This may also occur as a late complication of multiple myeloma. If there is a single plasma cell tumour (in bone or soft tissue) and the other features of myeloma are present, this is known as a solitary plasmacytoma (Kilciksiz et al, 2014).

Many signs of myeloma are related to the presence of paraprotein in the blood.
2012). Plasma-cell leukaemia and plasma-cytoma are relatively rare with complex management issues, which are not discussed in detail in this article. Management of secondary plasma cell leukaemia is no different than management of any other patient with advanced myeloma.

Epidemiology
Myeloma is a disease that generally affects people in later life, with only 15% of patients aged under 60 years. The incidence in the UK is about 60-70 per million per year, or about 4,500 new cases per year (Cancer Research UK, 2014). The condition is rare in Asian ethnic groups. It is approximately twice as common in Afro-Caribbean ethnic groups compared with Caucasians. Increasing age, male sex and the presence of a precursor condition (such as MGUS) are all associated with an increased risk of developing myeloma. Conditions that lead to immunosuppression, for example immunosuppression after solid organ transplant, increase the chance of developing myeloma (Passweg et al, 1996).

The only unequivocal external cause of myeloma is exposure to high levels of ionising radiation. Myeloma and related conditions are slightly more commonly seen in first-degree relatives of patients, which is consistent with the existence of susceptibility genes. This is supported by recent research identifying a number of gene variants capable of increasing the risk of developing myeloma (Chubb et al, 2013). However, neither MGUS nor myeloma are inherited conditions. The gene variants lead to a slightly increased risk of developing myeloma and individual family members are still at very low risk - scarcely higher than that of the general public.

Pathophysiology
Paraproteinaemia
Many myeloma signs are related to the presence of paraprotein in the blood. This is composed of a heavy chain and light chains - these are normal components of antibody molecules. There are five different types of heavy chain, known as IgM, IgG, IgA, IgD and IgE. Myeloma can be classified by the type of heavy chain involved – IgG is the most common. Light chains are either K (kappa) or λ (lambda) and in approximately 20% of cases only light chains are present, which can be detected by a specific test (Bird et al, 2013). The presence of paraprotein is generally considered a defining feature of myeloma, although a small proportion of cases have no detectable paraprotein. This is known as non-secretory myeloma and is managed in the same way as other cases, although monitoring is more difficult (Lonial and Kaufman, 2013).

Bone destruction
A high proportion of patients develop sites of bone destruction (lytic lesions). These usually appear in a number of sites, which is why the condition may be referred to as multiple myeloma. Myeloma cells interact with bone marrow stroma, increasing the production of bone-destroying cells (osteoclasts) and inhibiting the activity of bone-producing cells (osteoblasts) (Raje and Roodman, 2011). Myeloma bone damage may lead to pathological fractures in long bones and to vertebral collapse. This may compromise the spinal cord and requires immediate treatment (Tosi, 2013).

Renal impairment
Renal impairment affects up to half of all patients with myeloma at some stage in their illness. Up to 40% will develop kidney impairment and 10-15% will need dialysis (Dimopoulos et al, 2010). This may be a consequence of paraproteinaemia leading to proximal tubular damage or to protein cast nephropathy. Other possible causes include hypercalcaemia, dehydration, hyperuricaemia, infection or the action of nephrotoxic drugs. Unfortunately, several of the drugs used to treat myeloma have an adverse effect on kidney function, which may influence the choice and dosage of drugs used (Dimopoulos et al, 2010).

Hypercalcaemia
Hypercalcaemia is a paraneoplastic condition that is associated with many forms of cancer. It is often particularly severe in myeloma because of the increased bone turnover. If severe, hypercalcaemia may be a medical emergency (Reagan et al, 2014).

Neuropathy
Neuropathy may be present at diagnosis, and can be either paraprotein related or due to comorbidity. It may be exacerbated by neurotoxicity of drugs that are commonly used in treatment of myeloma (Snowden et al, 2011).

Signs and symptoms
Myeloma can present in a number of guises (Talamo et al, 2010). Some patients are asymptomatic, with abnormalities being identified as a result of routine screening or investigations in connection with another illness. Where symptoms are present, these may include ( singly or in combination) the CRAB features described. However, certain other features have been considered to be “red flags” for a myeloma diagnosis in patients who have back pain, including (George and Sadovsky, 1999):
- Aged over 50 years;
- Pain that is worse in supine position;
- Pain that is worse at night or awakens patient from sleep;
- Pain with a band-like distribution around the body;
- Pain that is not relieved with conventional methods (rest, non-steroidal anti-inflammatory drugs);
- Associated constitutional symptoms (fever, weight loss, dehydration);
- Progressive neurologic deficit in lower extremities;
- Peripheral neuropathy.

Diagnosis
At an incidence of 60-70 per million per year, a GP with a list of 2,000 patients might expect to see one new myeloma patient every 10 years or less. Over that period the same GP will have seen thousands of adult patients with back pain, anaemia and persistent malaise; this explains why many patients with myeloma have a history of chronic symptoms before being diagnosed. There is clear evidence that patients with myeloma experience longer diagnostic delays than those with other forms of cancer and this has not improved following cancer referral guidance from the National Institute for Health

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>DIFFERENTIATION BETWEEN MGUS, SMOULDERING MYELOMA AND MYELOMA</th>
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<tbody>
<tr>
<td></td>
<td>MGUS</td>
</tr>
<tr>
<td>Serum M protein</td>
<td>&lt;30 g/l</td>
</tr>
<tr>
<td>Clonal plasma cells</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>CRAB* features</td>
<td>Absent</td>
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<tr>
<td>Management</td>
<td>Watch and wait</td>
</tr>
</tbody>
</table>

*CRAB features: raised Calcium levels, Renal abnormalities, Anaemia or Bone damage. MGUS = monoclonal gammopathy of undetermined significance

“The parents of children with disabilities should not have to fight to get services”
Bernie Carter p25

www.nursingtimes.net / Vol 110 No 34/35 / Nursing Times 20.08.14 13
First-line treatment typically uses a combination of cytotoxic chemotherapy (cyclophosphamide or melphalan), a steroid (dexamethasone or prednisolone) and a novel agent. Melphalan is less commonly used because it may cause cytopenia and will compromise stem-cell collection if HDT-SCT is planned. The term “novel agents” is, in some cases, misleading as several of these drugs have been in use for some time. Novel agents include:
- Immunomodulatory drugs (IMiDs) – thalidomide, lenalidomide, pomalidomide (available via the Cancer Drugs Fund);
- Proteasome inhibitors – bortezomib;
- Drugs that are under development or undergoing clinical trials – carfilzomib, daratumumab, elotuzumab, ixazomib citrate, panobinostat.

First-line treatment is divided into three phases: remission induction, consolidation and maintenance. HDT-SCT is considered a form of consolidation. Chemotherapy-only consolidation and maintenance are not routinely used outside of clinical trials in the UK. In patients who are older or less fit, similar drug combinations are used but often at attenuated dosages.

Myeloma is a relapsing/remitting disorder and all patients will experience relapse, even after very successful first-line treatment (Fig 1).

**Treatment of relapse**

The choice of treatment at relapse depends on a number of factors, including:
- Age and fitness for intensive treatment/ HDT-SCT;
- Duration of remission;
- Treatments already received.

At first relapse, if the initial remission has lasted at least a year (Smith and Yong, 2013), retreatment with the same, or a similar, regimen is likely to be successful. If the first remission has been brief or following a second or further relapse, additional agents may be added. In virtually all cases, if the patient survives long enough, refractory relapse will occur.

**Treatment of refractory myeloma**

Primary refractory myeloma is not common. Eventually most patients will develop a refractory relapse that does not respond to any standard protocol. Options for treatment of primary refractory myeloma or refractory relapse include:
- Try a different treatment;
- Escalation of treatment as for early or repeated relapse;
- Clinical trial – this is a good option, if available, as newer drugs can still be effective.

**Ongoing care after treatment**

All patients with myeloma require supportive care. This is of critical importance in improving survival and quality of life for this group. Nurses play a vital role in patient education and in the early recognition of complications, such as infections or thrombosis, which need emergency treatment.

The BCSH has published a guideline on the supportive care of patients with myeloma (Snowden et al, 2011). This covers:
- Infection;
- Anaemia;
- Haemostasis and thrombosis issues;
- Pain management;
- Peripheral neuropathy;
- Other symptom control – gastrointestinal, sedation/fatigue, mucositis;
- Complementary therapies;
- End-of-life care.

Myeloma and its treatment both lead to impaired immunity, rendering patients vulnerable to infection. Patient education, as well as access to 24-hour specialist advice and treatment, is crucial in preventing and managing infection (Snowden et al, 2011). Anaemia is common in myeloma and may be caused by the disease itself, by renal impairment or as a side-effect of chemotherapy. It may require blood transfusion and/or treatment with erythropoiesis-stimulating agents (Myeloma UK, 2012).

Myeloma increases the risk of venous thromboembolism (VTE) and certain drugs used to treat myeloma exacerbate this risk (Cesarmian-Maus et al, 2012). Depending on the estimated risk, prophylaxis may be achieved with aspirin or may require heparin or warfarin. Major spontaneous bleeding is uncommon in patients with myeloma or related conditions (Eby, 2007).

Pain may occur due to bone disease or neuropathy. Severe bone disease has become less common since the...
introduction of bisphosphonates. Peripheral neuropathy may be present at diagnosis or may be triggered or exacerbated by treatment. If iatrogenic, neuropathy may be improved by changing the drugs and/or dosage. Transcutaneous electrical nerve stimulation may be effective in controlling neuropathy and, in some cases, pain-relieving drugs may be beneficial. NSAIDs should be avoided because of the risk of triggering or exacerbating renal impairment.

**Long-term complications**

**Peripheral neuropathy**

Peripheral neuropathy may occur as a feature of myeloma itself, as a result of comorbidity or may be iatrogenic. Certain drugs may cause neuropathy or may exacerbate existing neuropathy. It is important that patients are aware of the features of neuropathy, as reducing the drug dose or changing treatment may be necessary to avoid severe, irreversible neuropathy (Morgan, 2012).

**Renal failure**

Up to 40% of patients with myeloma will develop renal impairment and 10-15% will require dialysis (Leung and Nasr, 2014). Correction of renal impairment impinges on the overall survival probability and has a major effect on quality of life, but the risk of renal impairment may be decreased by precautions, such as ensuring patients have adequate fluid intake (at least three litres daily) (Dimopoulos et al., 2010).

**Thrombosis**

As with neuropathy, thrombosis may be part of the disease process, a consequence of comorbidity or a complication of treatment. Unlike with solid tumours, however, thrombosis in myeloma appears not to impact on survival. Iatrogenic thrombosis is a particular feature of regimens that combine IMiDs with dexamethasone. In any case, thrombosis in myeloma appears not to impact on survival. Iatrogenic thrombosis in myeloma appears not to impact on survival. Iatrogenic thrombosis in myeloma appears not to impact on survival.

**Amyloidosis**

Amyloidosis or primary systemic amyloidosis, affects about 10% of patients with myeloma (International Myeloma Working Group, 2003). In some cases, the paraprotein consists of light chains that have the capacity to form insoluble fibrils, which can deposit in many different tissues of the body and cause local tissue damage. The primary objective of treatment for these patients remains control of the myeloma as this will block further production of amyloid fibrils.

**Nursing care**

Myeloma treatment includes: multi-drug chemotherapy regimens, which work synergistically; supportive treatments, such as bisphosphonates to protect against bone damage; and prevention and management of infection. Therefore, treatment plans are complex and present challenges to nurses and other health professionals caring for patients with myeloma. Treatment may result in an accumulation of toxicities, which themselves need to be monitored and managed (Kurtin and Faiman, 2013).

Myeloma occurs mainly in older people and comorbidity is common. Therefore, non-specialist nurses may find themselves involved in the care of patients who have myeloma. It is important to establish contacts with specialist colleagues, who can advise on patients’ specific myeloma-related needs. Specialists can also offer advice and guidance on the warning signs of myeloma-related complications or on signs that the disease is progressing.

**References**


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