Chapter 13

Pain and Multiple Myeloma

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1. Introduction

Multiple myeloma is a plasma cell malignancy characterized with clonal expansion of malignant plasma cells within the bone marrow and followed by osteolytic bone disease. It accounts for approximately 1% of all malignant diseases and represents about 10% of hematologic malignancies. Data from cloning and gene-sequencing studies strongly imply that the malignant clone in MM arises from a late cell in B-cell development. Investigation of a patient with suspected myeloma should include the screening tests. Electrophoresis of serum and concentrated urine should be performed, followed by immunofixation to confirm and type any M-protein present.

The common clinical presentations are fatigue and bone pain with or without associated fractures or infection. Mechanical impacts like intraosseous tumor pressure, microfractures, periost irritation, muscle spasm, nerve entrapment and compression of nerves by the collapsed vertebrae are reasons of severe myeloma pain.

Radiographic skeletal survey and bone marrow aspiration and biopsy are performed for diagnosis. Angtuaco EJ et al reported a radiologic review and explained that MR imaging bone marrow surveys in patients with MM demonstrate the broad spectrum of involvement, the results of treatment, the areas of potential complications, and the sites of focal disease for safe bone biopsies [1].

Pain characteristics clinically can be summarised as, pain is worse in supine position, especially at night or awakens from sleep, band like distribution around body, not relieved with rest and nonsteroidal anti-inflammatory drugs (NSAIDS), associated symptoms like fever, weight loss and progressive neurologic deficite in lower extremities. Somatic, visceral and neuropathic components can be easily involved in myeloma pain [2].

Chronic pain is extremely prevalent among patients with cancer. According to studies cancer pain can be relieved in more than 70% of patients using a simple opioid- based regimen.

Whether there is a relatively lesser degree of opioid responsiveness in chronic cancer pain, then adjuvant analgesics are neccessary. Adjuvant analgesics describe the drug with a primary indication other than pain, but with analgesic properties in some painful conditions, they are usually coadministered with analgesics (acetaminophen, NSAIDS, opioids) when treating cancer pain. Common causes of chronic pain in cancer patients as multiple myeloma patients are releated to peripheral neuropathy due to chemotheraphy, radiotheraphy and tumor invasion, chronic postsurgical incisional pain, phantom pain, musculoskeletal pain, visceral pain from viscera or tumor.

The pain is one of the most common symptoms at diagnosis experienced by myeloma patients and it may also be an indicator of a subsequent relapse. Up to 67% of patients report pain at diagnosis, although this may have been present for several months before [3]. At diagnosis, pain may be due to the disease process itself (predominantly from destructive bone disease, but occasionally from plasmacytomas directly affecting neural tissues), or it may signify a co-morbidity (e.g. degenerative arthritis or osteoporosis).

Later in the course of the disease, pain often arises as a sideeffect of therapies, e.g. thalidomide or bortezomib neuropathy. Particularly in older patients, it is important to always consider co-morbidities, such as arthritis or osteoporosis, mimicking bony malignant pain; diabetes or carpal tunnel syndrome mimicking peripheral neuropathy (PN); and postherpetic neuralgia as a common cause of persistent pain.

Assessment of pain, should start with taking a history but may involve imaging by X ray, bone scan, CT or MRI. Myeloma patients should be evaluated for the presence and severity of pain regularly. Pain severity can be assessed by visual analogue scales (VAS), numerical rated scales (NRS) or verbal rated scales (VRS) [4]. To diagnose the presence of neuropathic pain, the Leeds assessment of neuropathic symptoms and signs scale (LANSS) can be used [5].

The pain is usually in constant and dull at first but, as the disease progresses, it becomes more severe until it is agonizing and constant. Severity of pain may be particularly devastating and can negatively affect the quality of patient life and their functional status. This should be managed using a multi-modal, mechanism-based approach including evidence-based pharmacological therapies alongside non-drug methods such as radiotherapy, bisphosphonates, and where appropriate, interventional and psychological techniques.

The critical importance of pain management as part of routine cancer care has been forcefully advanced by WHO, international and national professional organisations, and governmental agencies.

American Pain Society Quality of Care Task Force reviewed recommendations for faciliating improvements in the quality of cancer pain management.

- Recognize and treat pain promptly (emphasis on comprehensive assessment and importance of preventive and prompt treatment based on evidence for neuroplasticity)
- Involve patients and families in pain management plan (emphasis on customization of care and participation of patient in treatment plan)

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- Improve treatment patterns (eliminate inappropriate practices, provide multimodal therapy)
- Reassess and adjust pain management plan as needed (respond not only to pain intensity but to functional status and side effects)
- Monitor processes and outcomes of pain management (new standardized indicators and comments about forthcoming national performance indicators)

According to the European Society of Medical Oncology (ESMO) clinical practice guidelines with WHO ladder, general approach to management of cancer pain is,

STEP I: Mild pain (NRS: 1–4) is treated with non-opioid analgesics such as acetaminophen/ paracetamol or a NSAID

Paracetamol is a useful analgesic in cancer-related pain and other chronic pains and should be prescribed at a dose of up to 1 gram qid (p.o. or i.v. in patients who cannot take oral medication, e.g. because of vomiting or mucositis).

NSAIDS should be avoided apart from very short term use (eg 3-5 days) with acute severe pain, eg bone fracture. They should not be used in the presence of renal impairment, and used with extreme caution in myeloma patients in view of the risk of precipitating renal compromise

For patients with mild pain (<5/10), normal release tramadol is a reasonable choice of analgesic agent. Tramadol has 1/5th the potency of oral morphine and the starting dose is 50mg 6 hourly prn or qid. Codeine can also be used but it is a pro-drug of morphine, and 10-15% of the population is unable to convert it into active morphine, leaving them with unacceptable toxicity [6].

STEP II: Traditionally, patients with moderate pain (NRS: 5–7) have been treated with a combination product containing acetaminophen plus a weak immediate-release opioid

For patients with mild to moderate pain or whose pain is not adequately controlled by paracetamol or a NSAID given regularly by mouth, the addition of a step II opioid (eg, codeine or tramadol; table 1) given orally might achieve good pain relief without troublesome adverse effects. Alternatively, low doses of a step III opioid (eg, morphine or oxycodone; table 1) may be used instead of codeine or tramadol.

STEP III: In severe pain (NRS: 8–10), morphine, oxycodone, and hydromorphone can use and the data show no important differences between morphine, oxycodone, and hydromorphone given by the oral route. Morphine is most commonly used. Oral administration is the preferred route. If given parenterally, the equivalent dose is one-third of the oral medication. The buccal, sublingual and nebulized routes of administration of morphine are not recommended because at the present time there is no evidence of clinical advantage over the conventional routes.

Patients with chronic moderate (5-7/10) or severe pain (>7/10) can be started on tramadol as above, but will usually need to go onto more potent opioids rapidly if they do not respond. Hydromorphone or oxycodone, in both immediate-release and modified-release formulations for oral administration are effective alternatives to oral morphine. Oxycodone is twice the

Oral opioid	Characteristics and comments
Codeine	Step II drug only: use alone or in combination with paracetamol; daily doses ≥360 mg not recommended
Tramadol	Step II drug only: use alone or in combination with paracetamol; daily doses ≥400 mg not recommended
Hydrocodone	Step II drug only: used as a substitute for codeine in some countries
Oxycodone	Step II opioid when used at low doses (eg, ≤20 mg per day) alone or in combination with paracetamol
Morphine	Step II opioid when used at low doses (eg, ≤30 mg per day)
Hydromorphone	Step II opioid when used at low doses (eg, ≤4 mg per day)

Table 1. Step II opioids

potency of morphine and is associated with less drowsiness and hallucinations. For rapid onset, the normal release preparation can be used 4-6 hourly or qid, but most patients eventually prefer the convenience of the bd sustained release forms [7].

Methadone is a valid alternative but may be more complicated to use because of marked inter-individual differences in its plasma half-life and duration of action. Methadone use should be initiated by physicians with experience and expertise in its use. Strong opioids may be combined with ongoing use of a nonopioid analgesic (step I). Patients presenting with severe pain that needs urgent relief should be treated with parenteral opioids, usually administered by the subcutaneous (s.c.) or intravenous (i.v.) route. Intramuscular injections are painful and have no pharmacokinetic advantage.

Patches can be used to deliver either fentanyl or buprenorphine, both of which are very potent opioids. Fentanyl causes significantly less nausea, sedation and constipation compared to morphine [8]. When given the choice of fentanyl patches or oral morphine for chronic pain, patients prefer the patches [9]. They are usually the treatment of choice for patients who are unable to swallow, patients with poor tolerance to morphine and patients with poor compliance. Earlier worries regarding an inferior equipotency ratio of buprenorphine to oral morphine or of a ceiling effect and partial antagonistic effects of buprenorphine as compared with fentanyl have not been substantiated by newer publications [10]. Buprenorphine often initially causes nausea but this can be covered by the use of an anti-emetic such as metoclopramide and is otherwise well tolerated.

Immediate-release and slow-release oral formulations of morphine, oxycodone, and hydromorphone can be used for dose titration. The titration schedules for both types of formulation should be supplemented with oral immediate-release opioids given as needed. When using normal release oral medication, the dose can be titrated up daily by 30-50% until pain is controlled or unacceptable side effects occur. With sustained release oral medication it is

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advisable to wait 2-3 days between dose increments. With patches, doses should not normally be increased at less than 3 days intervals.

With all sustained release analgesics, it is essential to offer the patient a normal release 'rescue medication' for breakthrough pain. This is particularly important when breakthrough pain occurs quickly and predictably. It is important to distinguish this kind of 'incident pain' from pain arising from end of dose failure with sustained release medications, or spontaneous pains associated with neuropathy or opioid-induced hyperalgesia [11]. The 'breakthrough dose' is usually equivalent to +10% - 15% of the total daily dose. If more than four 'breakthrough doses' per day are necessary, the baseline opioid treatment with a slow-release formulation has to be adapted. Normal release oxycodone or morphine can be used, at 1/6th of the current 24 hour total opioid dose. However, often the absorption of these oral drugs can be too slow for breakthrough pain.. Opioids with a rapid onset and short duration are preferred for breakthrough doses. Fentanyl has a high bioavailability via the transmucosal route, which has led to the development of fast-acting (but short-lived) fentanyl formulations. These include fentanyl lozenges (Actiq ®); buccal tablets (Effentora®); or sublingual tablets [12]. Nasal sprays will also soon be available. Normally, a patient should not need to use more 2–3 of these relatively expensive fentanyl formulations per day for breakthrough pain; if more are being taken, either the background medication needs to be increased or the patient should be referred to a specialist. There is no place for pethidine in the treatment of pain in myeloma.

In addition, there is also worth noting that the recommendations for opioids for breakthrough of the EAPC. The pain exacerbations resulting from uncontrolled background pain should be treated with additional doses of immediate-release oral opioids, and that an appropriate titration of around-the-clock opioid therapy should always precede the recourse to potent rescue opioid analgesics. Breakthrough pain (eg, incident pain) can be effectively managed with oral, immediate-release opioids or with buccal or intranasal fentanyl preparations. In some cases the buccal or intranasal fentanyl preparations are preferable to immediate-release oral opioids because of more-rapid onset of action and shorter duration of effect. Additionally, immediate-release formulations of opioids with short half-lives should be used to treat pre-emptively predictable episodes of breakthrough pain in the 20–30 min preceding the provoking manoeuvre.

With all opioids, it is important to offer the patient a laxative and to keep checking for the development of constipation. Transdermal fentanyl and buprenorphine are associated with reduced incidence of constipation [13]. It is not necessary to routinely prescribe an anti-emetic with opioids, except for the first week when starting buprenorphine.

Respiratory depression is uncommon in patients treated chronically with opioids as long as dose increments are made carefully as outlined above. With the initiation of opioids, it is common to see a reduction in respiratory rate; however, this is usually balanced by changes in tidal volume so that minute ventilation initially remains steady. Care needs to be taken in patients with COPD or obstructive sleep apnoea, in whom the respiratory depression can occur even with low doses of opioids. True respiratory depression caused by opioids is diagnosed by a reduction in oxygen saturation ($SaO_2 < 90\%$) or by arterial blood gases. If this occurs, naloxone can be given but care must be taken not to provoke a serious increase in pain. Advice on future opioid dosing should be sought from a specialist in pain or palliative medicine.

Recently a condition known as opioid-induced hyperalgesia has been consistently identified in animal studies and has also been demonstrated to occur in human studies. This condition is characterised by increasing reporting of pain in the presence of increasing opioid dosage. The pain can be localised to the original lesion but is often generalised to adjacent dermatomes. The skin in the affected area may show hyperalgesia (increased pain response on normal painful stimulus) or allodynia (pain felt even on light touch). The treatment involves reduction in the opioid dosage along with the introduction of an NMDA channel blocker such as ketamine or methadone [14].

Most opioids cause dose-related sedation; however, fentanyl and oxycodone are associated with reduced sedation compared to morphine [15]. Patients who experience intolerable sedation due to opioids (or other drugs, e.g. thalidomide) may be considered for a trial of a psychostimulant such as methylphenidate or modafanil; this should only be prescribed by a specialist in palliative medicine. In patients with opioid-related neurotoxic effects (delirium, hallucination, and myoclonus), dose reduction or opioid switching should be considered.

Patients receiving step III opioids who have side-effects and do not achieve adequate analgesia that are severe, unmanageable, or both, might benefit from switching to an alternative opioid.

When switching from one opioid drug to another, dose conversion ratios can be recommended with different levels of confidence (table 2). These conversion ratios are specific for patients in whom analgesia from the first opioid is satisfactory. Therefore, when the opioid is switched because of unsatisfactory analgesia, excessive side-effects, or both, clinical experience suggests that the starting dose should be lower than that calculated from published equianalgesic ratios. In all cases the dose needs to be titrated in accordance with clinical response.

For patients with continuing severe (>6/10) pain or those who are unable to tolerate analgesics because of adverse effects, help should be sought from a specialist service such as the palliative care team or chronic pain team.

Haematology teams should readily seek to share care of pain and other symptoms with local palliative and supportive care teams. Patients at home can be seen by community or hospice-based palliative care teams. Hospital chronic pain teams should be consulted for severe pain if palliative and supportive care teams are not available. Acute pain teams may be helpful if the patient has an acute severe pain, e.g. bone fracture causing immobilization, which may respond to interventional procedures, e.g. local nerve blockade or spinal delivery of opioids and local anaesthetic. Orthopaedic surgeons or interventional radiologists are able to perform cement vertebroplasty or kyphoplasty for uncontrolled pain arising from vertebral collapse. Psychologists can help with patients who have severe anxiety overlying pain and with other issues.

In many of multiple myeloma patients, musculoskeletal complications with enhanced bone destruction lead to pain with pathologic fractures, spinal cord compression and radiculopathy. Bone lesions result not only from the direct deposits of myeloma cells within the bone, but also from the release of soluble factors by both the tumor and the microenvironment, resulting in the stimulation of osteoclast activity and bone resorption. The inhibition of bone resorption and hypercalcaemia can be reduced by the use of bisphosphonates. This class of drugs

RELATIVE ANALGESIC RATIO	STRENGTH OF THE RECOMMENDATION FOR USE	
Oral morphine to oral oxycodone	1.5 : 1	Strong
Oral oxycodone to oral hydromorphone	4 : 1	Strong
Oral morphine to oral hydromorphone	5 : 1	Weak
Oral morphine to TD buprenorphine (*)	75 : 1	Weak
Oral morphine to TD fentanyl (**)	100 : 1	Strong

(*) Example: 60 mg oral morphine to 35 µg/h TD buprenorphine (equivalent to 0.8 mg per 24 h).

(**) Example: 60 mg oral morphine to 25 µg/h TD fentanyl (equivalent to 0.6 mg per 24 h).

TD=transdermal.

Table 2. Relative analgesic dose ratios

potentiate the effects of analgesics in improving myeloma bone pain with reducing bone releated events, but not mortality.

Management of spinal pain is often conservative, in the absence of instability/neurological compromise, orthopaedic, neurosurgical or interventional radiological advice should be sought in cases of persistent/refractory pain. Vertebroplasty and kyphoplasty are alternative options for controlling pain associated with vertebral collapse. Vertebroplasty and kyphoplasty are both vertebral body augmentation techniques of percutaneous injection of bone cement to the vertebral bodies. They are best performed soon after the vertebra collapses and may be ineffective if many months have elapsed. Both techniques carry the small risk of cement leakage leading to pulmonary embolism and neural compromise. It is therefore important that there is access to a spinal surgery service when these procedures are performed.

Vertebroplasty involves the percutaneous injection, under general anaesthetic and i.v. sedation and using radiological imaging, of polymethacrylate bone cement or equivalent biomaterial into the vertebral body. Several vertebrae can be treated simultaneously. The injection allows local pain relief and bone strengthening but will not restore vertebral height. No randomized studies on the use of vertebroplasty in myeloma have been published. However, a recent review of 67 cases demonstrated improvements in pain (89%), mobility (70%) and use of opioid analgesia (65%) [16].

Kyphoplasty involves the percutaneous insertion of a small, inflatable balloon into the vertebral body; when inflated it produces a potential space. The balloon is then removed and bone cement is injected to fill the cavity. Although more time consuming than vertebroplasty the complication rates appear lower with similar potential benefits of both pain relief and

improved function to vertebroplasty but with reduced risk of cement leak. There is also the potential to restore vertebral height but this only occurs in a minority of patients. At the present time, the documented use of kyphoplasty in myeloma is limited to case reports and small case series although outcomes in myeloma do appear comparable to those in osteoporosis [17, 18].

Many patients with myeloma have subclinical or even clinical peripheral neuropathy (PN) at diagnosis, often due to co-morbidities. These patients are at risk of worsening PN when exposed to potentially neurotoxic drug treatments, such as thalidomide and bortezomib. The cause of PN in myeloma patients is multifactorial and when patients are assessed, it is important to grade the degree of neuropathy using a recognized scale, such as the National Cancer Institute (NCI), Common Toxicity Criteria [19], LANSS [20] or the Total Neuropathy Score [21].

PN in myeloma patients can be subdivided as follows:

- Disease- or M protein-associated peripheral neuropathy
- Peripheral neuropathy related to co-morbidities
- Chemotherapy-induced peripheral neuropathy

Disease- or M protein-associated peripheral neuropathy: Spinal cord or nerve root compression is a common neurological complication of myeloma due to compression by plasmacytoma, lytic or extramedullary disease and requires appropriate imaging and specific treatment including a specialist opinion as to the need for surgical intervention or radiotherapy.

The reported prevalence of sensory PN may depend on the study cohort, the methods of detection and the criteria used, with a recent study reporting rates of pretreatment sensory PN in up to 20% of patients, and neuropathic abnormalities in as many as 54%. [22].

The cause of the neuropathy in many cases of myeloma is not clear and may be multifactorial, and studies have also varied in relation to rates of small or large fibre or mixed PN. In those cases where amyloidosis and toxicity due to chemotherapy are not the cause, the M protein itself or other consequences of the underlying disease may play a part. Clinically, a symmetrical, distal sensory/motor neuropathy inducing paraesthesiae and numbness in the hands and feet is seen.

POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, M-protein and Skin abnormalities) syndrome and AL amyloidosis are more specialized situations, PN is a significant clinical feature in 85–100% of patients affected by POEMS syndrome [23]. It is a consequence of axonal degeneration and demyelination, typically distal, symmetrical and initially sensory, but as the condition progresses, a disabling symmetrical weakness may develop.

PN affects 17% of patients with AL amyloidosis at diagnosis. The PN is typically axonal and characteristically painful, distal and symmetrical and often associated with an autonomic neuropathy. Cryoglobulinaemia is another recognized source of PN.

Peripheral neuropathy related to co-morbidities: Conditions such as diabetes mellitus, carpal tunnel and other nerve compression syndromes, including chronic inflammatory demyelinat-

ing polyradiculoneuropathy, chronic renal failure and vitamin B12 deficiency, should be actively sought and appropriately managed, with specialist input as needed.

Chemotherapy-induced peripheral neuropathy: Chemotherapy-induced peripheral neuropathy (CIPN), also known as treatment-emergent peripheral neuropathy, is a major aspect of myeloma management. CIPN has been a long recognized complication of vinca alkaloid and platinum-based treatments and may be significantly dose limiting, but these drugs are no longer in regular use in myeloma. There is emerging evidence for the incidence and natural history of PN due to novel therapies, including thalidomide-induced PN (TiPN) and bortezomib-induced PN (BiPN), which may be considered as distinct clinical entities.

TiPN may arise after prolonged administration of thalidomide, is mostly mild to moderate in severity and appears to be a cumulative effect [24]. Initial symptoms include sensory changes, such as paraesthesia and hyperaesthesia, motor symptoms and autonomic dysfunction. Later effects include loss of vibration and joint position sense, which may lead to ataxia and progressive gait disturbance. Nerve conduction studies do not reliably predict the onset of significant TiPN and do not necessarily correlate with the clinical findings. Reduction or temporary discontinuation of the drug usually leads to a clinical improvement in the symptoms whereas continuation of dose intense treatment in the face of neuropathy may cause permanent neurological damage. Mileshkin et al and other investigators have recommended that thalidomide therapy should not exceed 6 months as the risk of TiPN is unacceptably high [25].

BiPN is characterized by neuropathic pain and a lengthdependent distal sensory neuropathy with suppression of reflexes. Motor neuropathy may follow and infrequently results in mild to severe distal weakness in the lower limbs. There may also be a significant autonomic component, which manifests as dizziness, hypotension, diarrhoea or constipation and/or extreme fatigue. It is thought to occur at a certain threshold (within five cycles but rarely beyond) of treatment and may be more likely to occur within the setting of renal impairment, in keeping with other therapy related toxicities in this setting. Electrophysiological testing reveals a mainly distal sensorimotor axonal loss, with secondary demyelination. The symptoms of BiPN improve or completely resolve in the majority of patients after a median of 3 months following discontinuation of the drug, but in a proportion of cases, symptoms have taken up to 2 years to improve [26]. Apart from a graded dose reduction or withdrawal [27], the only treatment for BiPN is symptomatic relief. No effective prophylactic treatment is available and any use of nutritional supplements should be restricted to low doses to avoid harm from excessive doses of pyridoxine. In particular, caution should be exercized with supplements containing ascorbic acid, which may inhibit the anti-myeloma effect of bortezomib [28].

An accurate neurological history should be taken from all patients prior to commencement of neurotoxic agents and regularly during the course of therapy. Patients should be reviewed in person at the start of each cycle to ensure that emergent symptoms are detected and acted upon. Dose-reductions may be needed within a treatment cycle if symptoms are progressive, so as to avoid the irreversible neurological damage that may result from waiting until the next cycle to make a change.

Initial investigations should be tailored according to the history and examination. Vitamin B12 deficiency should be screened for periodically. Metabolic and autoimmune causes should also

be considered. If there are prominent features of small fibre neuropathy, then AL amyloidosis should be excluded by tissue biopsy or serum amyloid P scan; any further investigations, such as electrophysiological studies or cerebrospinal fluid protein estimation, should be directed by a neurologist.

The management of PN should include symptom control along with treatment of any potentially reversible causes. Identification and correction of Vitamin B12 deficiency is important and optimal management of co-morbid causes, such as diabetes mellitus or alcohol excess, may also improve tolerance of neurotoxic drugs. An awareness of the spectrum of symptoms that herald CIPN is crucial. Such symptoms need to be carefully sought at each meeting with the patient.

Careful monitoring of patients receiving bortezomib and prompt dose and schedule modifications are essential. Temporary interruptions in therapy may also be beneficial, before resuming on a new schedule/dose. Recent data from front line protocols incorporating bortezomib suggest that a weekly regimen is as effective and associated with less neuropathy than twice-weekly regimens [29]. Although, the twice weekly regimens of subcutaneous bortezomib offers non-inferior efficacy to standard intravenous administration, with an improved safety profile for peripheral neuropathy in patients with relapsed multiple myeloma [30]. Continuation of dose intense treatment in the face of neuropathy may cause permanent neurological damage. Measurement of lying and standing blood pressures weekly in patients receiving bortezomib may detect autonomic neuropathy before it becomes a debilitating problem for the patient. The administration of intravenous normal saline prior to each dose of bortezomib may improve tolerance of the drug.

Neuropathic pain is often poorly responsive to standard analgesic regimes. There has been very little research specifically in the management of painful CIPN, and that has mostly been in solid tumours [31]. Opioids can be effective but if used alone in high dose are associated withsignificant adverse effects [32]. A multimodal approach using opioids together with other pain modulating drugs is now recommended [33]. Thus a calcium channel blocker should be added early (e.g. gabapentin or pregabalin); it may be necessary to add a sodium channel blocking agent, e.g. oxcarbazepine (carbamazepine should be avoided because of drug interactions); or an SNRI, e.g. amitryptiline or duloxetine.

Several studies have shown that adding gabapentin to an opioid in patients with cancer-related neuropathic pain can give improved analgesia with reduced adverse effects compared to using either agent alone [34]. The response to gabapentin correlated with the severity of the underlying neurotoxicity. Approximately 25% of patients receiving gabapentin experienced mild somnolence, but none discontinued it. Note that gabapentin may be associated with myelosuppression and so should be avoided around the time of stem cell transplant.

The haematologist who is not familiar with these agents should seek advice from the local chronic pain or palliative care service. For patients with continuing severe pain in spite of initiating these drugs or those who are unable to tolerate analgesics because of adverse effects, specialist help is essential. They will advise on dose modifications and can also initiate specialist options, such as ketamine, methadone or spinal analgesia.

In addition, topical treatments may be of benefit. Capsaicin cream 0.075% acts on peripheral nerve TRPV1 heat and pain receptors; menthol acts on TRPM8 receptors for cold and may both be helpful in patients with „cold" or „hot" dysaesthesia respectively [35]. Emollients, such as cocoa butter, may help some patients but the physiological mechanism is unclear. In other forms of superficial neuropathic pains (e.g. post-herpetic neuralgia or scar pain), the sodium channel blocker lidocaine can be used topically as a 5% plaster, applied to the affected area for 12 hours and then left off for 12 hours. Some patients obtain relief within a few days but the peak effect is reached with 2-4 weeks [36].

Complementary therapy can be defined as therapies that are used alongside, or integrated with, conventional health care. These differ from alternative therapies, which are designed to be used in place of conventional therapy. However, a clear definition of what constitutes complementary and alternative medicine has not yet been elucidated, and therefore discretion must be exercised when interpreting guidance pertaining to these therapies.

Complementary therapy has a role in the management of multiple myeloma when used as adjunct to conventional medicine. It improves patients' perceived quality of life and ability to cope with the effects of the disease. The development of an evidence-base to support complementary therapy use in myeloma is in the early stages of development.

Patients with myeloma may express preference for complementary therapy and place value in the role they have to play within the context of their cancer care plan – for the management of both the psycho-social and physiological effects associated with myeloma. Patients may value complementary therapy and the sense of control gained when they are used as part of their cancer treatment plan. Consequently, patient choice should be informed and respected by healthcare professionals in order to ensure the best overall treatment and care plan for myeloma is delivered.

There is a dearth of scientific evidence to support the effectiveness of complementary therapy in the management of myeloma; however, some studies have shown that complementary therapy can help patients with myeloma to: manage their symptoms, live with altered body image, promote relaxation, alleviate anxiety, reduce chemotherapy side-effects, improve sleep pattern, reduce stress and tension, reduce psychological distress/provide emotional support and improve well-being. Importantly, cancer patients using complementary therapy also perceive an improved quality of life.

Some complementary therapies, such as acupuncture, have been submitted to more rigorous evaluation and are acknowledged for their effective use in cancer treatment for the management of chemotherapy-associated nausea and vomiting. However, no convincing scientific-evidence has emerged to date that shows complementary therapy slows cancer progression [37].

The types of complementary therapies and frequency with which they are used by myeloma patients vary considerably. Among the most common therapies are homoeopathy, touch therapies such as aromatherapy, massage and reflexology, healing and energy therapies such as reiki, spiritual healing and therapeutic touch, hypnosis and hypnotherapy, acupuncture, herbal medicines and dietary interventions [38].

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