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Nursing support during treatment of multiple myeloma with proteasome inhibitors

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Abstract

In the past two years proteasome inhibitors have risen in prominence reflecting the recent approval of two new agents, carfilzomib and ixazomib. This means there are three different agents of this class available for the treatment of multiple myeloma. These agents are highly effective and suitable for use in combination with other agents, however each has a different route of administration and an individual toxicity profile. Optimal patient management is required to use these agents to their full potential.

Nurses are instrumental in educating patients about these treatment options and managing their individual toxicities during treatment. They also play a crucial part in supporting ongoing communication between patients and the multidisciplinary team. To succeed in this role, nurses require a thorough understanding of evidence-based symptom-management programmes, and a good awareness of the efficacy and safety profiles of newer drugs. Time should be set aside for nurses to be educated and trained appropriately on topics identified in this review, and initiatives such as local myeloma learning programmes may be useful. This article discusses the central role of nurses in the management of proteasome inhibitors for the treatment of patients with multiple myeloma.

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Keywords

blood cancers, cancer, cancer treatments, communication, patients, patient education

Introduction

Multiple myeloma, although rare, is the second most common haematological malignancy (Siegel et al 2015) with an incidence of approximately five cases per 100,000 people per year (Ferlay et al 2012). In the UK the incidence in 2014 was 9.30 per 100,000 people per year, and this is expected to increase to 12 cases per 100,000 people by 2035 (Cancer Research UK 2018). Initial treatment is generally effective in achieving remission, but most patients eventually relapse and the remission period is typically followed by relapsed and/or refractory (RR) multiple myeloma (Campbell 2014) (Figure 1). The treatment landscape and disease course for multiple myeloma have changed significantly over the past couple of decades with patients surviving much longer (Kyle and Rajkumar 2008, Ludwig et al 2014), so patient pathways are often long and complex. Nurses play a vital role in supporting patients at each disease stage.

The National Institute for Health and Care Excellence (NICE) (2012) recommends shared decision-making, adding that nurses can support patients' contributions to treatment decision-making throughout treatment pathways, and ensure that effective communication takes place between patients and their oncologists or haematologists. During the early stages of treatment, decisions are likely to be driven by guideline recommendations and doctors' experiences, and nurses can help maintain positive and collaborative communication during this period to ensure patients' needs are met.

One of the most important roles for nurses in the management of people with multiple myeloma concerns relapsed disease. Treatment choice at relapse can be less clear than at first line due to the range of regimens available and the lack of established treatment algorithms. Guidelines, such as those by the British Society for Haematology (Bird et al 2014), recommend

that the most appropriate management should be determined on an individual basis, depending on the timing of relapse, age, previous therapy, bone marrow function, co-morbidities and patient preference (Bird et al 2014).

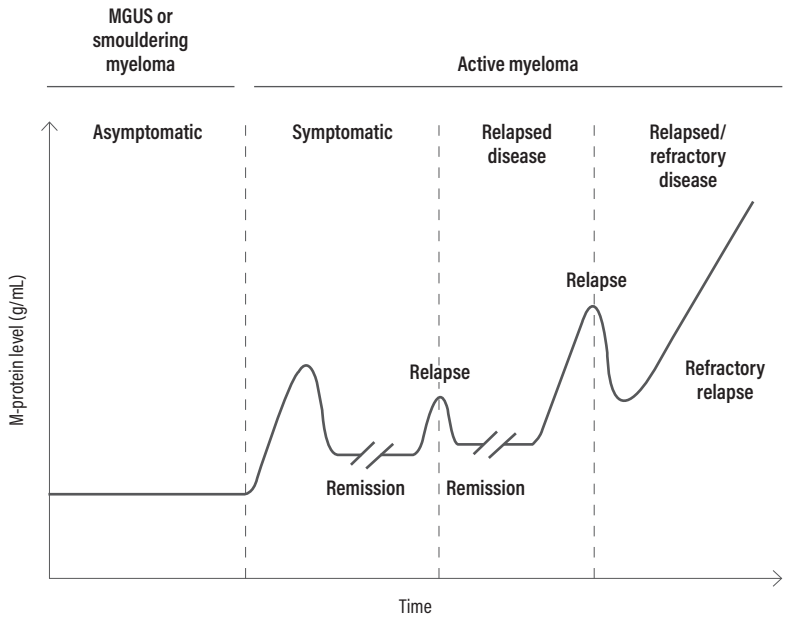
Nurses can help support the decision-making process by ensuring that patients' perspectives are shared with the multidisciplinary team (MDT), and that parameters such as quality of life are considered and assessed using validated tools, such as the Myeloma Patient Outcome Scale (Osborne et al 2015). Nurses can also offer a sensitive approach to managing complex emotions at this stage. For example, fear and uncertainty may be offset by some sense of relief at regaining control through reinitiating treatment. Furthermore, nurses can support patients who decide to discontinue active treatment and receive palliative care, for example with relief from the symptoms, pain and stresses associated with multiple myeloma during the RR period.

Potential therapies for use at relapse include immunomodulatory agents, such as thalidomide, lenalidomide and pomalidomide; histone deacetylase inhibitors, such as panobinostat; and monoclonal antibodies, such as daratumumab and elotuzumab. In addition, several proteasome inhibitors are available for the treatment of multiple myeloma. The first proteasome inhibitor to be available in Europe for multiple myeloma was bortezomib (Janssen-Cilag International NV 2017), which was initially approved in 2004. In the past two years this class of agent has risen in prominence with the approval of two additional proteasome inhibitors, carfilzomib and ixazomib (Amgen 2017, Takeda Pharmaceuticals 2017).

Table 1 details proteasome inhibitors for RR multiple myeloma that are approved or in development in Europe. There is a particular interest in the effect of proteasome inhibitors on patient outcomes due to their effectiveness and suitability for use in combination with other therapeutic agents (Merin and Kelly 2014). NICE (2007, 2017) recommends using carfilzomib with dexamethasone for patients who have not previously received bortezomib, or bortezomib monotherapy at first relapse. Although proteasome inhibitors are efficacious there can be side effects requiring interruption or cessation of anticancer therapy. These are often manageable and a thorough understanding of optimal supportive care can help patients remain on treatment and receive the maximum benefit from their therapy.

This article provides an overview of nurses' roles in the evolving management of patients with multiple myeloma and focusing on proteasome inhibitors. This knowledge will help to support appropriate monitoring of patients for signs and symptoms, and prompt timely and effective communication with patients.

Figure 1. Typical disease course in multiple myeloma



MGUS, monoclonal gammopathy of undetermined significance.
(Campbell 2014)

TABLE 1. Development status of proteasome inhibitors for multiple myeloma

Compound	Company	Route of administration	Development phase
Bortezomib (Janssen-Cilag International NV 2017)	Janssen-Cilag International NV (Beerse, Belgium) and Millennium Pharmaceuticals. (Cambridge MA)	Intravenous (IV) or subcutaneous	Approved
Carfilzomib (Amgen 2017)	Amgen Europe BV (Breda Netherlands)	IV	Approved
Ixazomib (MLN9708) (Takeda Pharmaceuticals 2017)	Millennium Pharmaceuticals. (Cambridge MA)	Oral	Approved
Marizomib (NPI-0052) (ClinicalTrials.gov 2016a)	Triphase Accelerator Corporation (San Diego CA)	IV	Phase1-2
Oprozomib (ONX-0912) (ClinicalTrials.gov 2016b)	Onyx Pharmaceuticals. (San Francisco CA)	Oral	Phase 1-2

Role of proteasome inhibitors in multiple myeloma

Proteasome inhibitors can be incorporated into the first-line treatment of multiple myeloma. For patients eligible for autologous stem cell transplantation (auto-SCT) induction, therapy typically involves administration of a combination of drugs (Moreau et al 2013, Ludwig et al 2014). Three-drug combinations recommended in Europe include those that incorporate proteasome inhibitors – bortezomib and dexamethasone plus one other drug (cyclophosphamide, doxorubicin, lenalidomide or thalidomide) (Moreau et al 2013, Ludwig et al 2014). In the UK, bortezomib with dexamethasone alone or plus thalidomide is recommended (NICE 2014). Three to four courses of induction therapy are recommended with the aim of achieving at least a partial response before proceeding to stem cell collection and high-dose chemotherapy (Moreau et al 2013).

Some patients may not be eligible for auto-SCT and for these individuals European guidelines recommend first-line treatment with melphalan and prednisone combined with thalidomide or bortezomib (NICE 2011, Moreau et al 2013).

Unfortunately, relapse of multiple myeloma, even following apparently successful induction treatment, is experienced eventually by most patients. At relapse, decisions need to be made about whether alternative treatment options can be tried or whether existing treatment should be escalated (Campbell 2014). Although many doctors prefer to use a new class of agent at each line to avoid inducing resistance, in practice patients may receive the same agent in multiple therapy lines, particularly in countries where not all novel drugs are fully reimbursed and may therefore be at risk of cumulative toxicity.

Bortezomib, carfilzomib and ixazomib are approved for treating patients at second line and later, but their use is not interchangeable. While there are many similarities between adverse events (AEs), not all occur to the same degree with each drug. The route of administration also varies: bortezomib can be administered intravenously (IV) or subcutaneously, with each route associated with a slightly different AE profile; carfilzomib is given IV; and ixazomib is administered orally (Amgen 2017, Janssen-Cilag International NV 2017, Takeda Pharmaceuticals 2017). An awareness of the different drug profiles is crucial for making informed decisions about the most appropriate treatment for each patient. Further, the drug combinations and doses approved in Europe differ for each agent (Table 2).

TABLE 2. Approved dosing regimens for the use of proteasome inhibitors for relapsed multiple myeloma in Europe

Compound	Drug combination	Required dose	Accompanying agents
Bortezomib (Janssen-Cilag International NV 2017)	Monotherapy	1.3mg/m^2 body surface area on days 1, 4, 8 and 11 in a 21-day cycle	N/A
	With doxorubicin		30mg/m^2 intravenously (IV) on day 4
	With dexamethasone		20mg orally on days 1, 2, 4, 5, 8, 9, 11 and 12
Carfilzomib (Amgen 2017)	With dexamethasone	20mg/m^2 in cycle 1 on days 1 and 2. If tolerated, the dose should be increased on day 8 of cycle 1 to 56mg/m^2 Given on days 1, 2, 8, 9, 15 and 16 in a 28-day cycle	20mg orally or IV on days 1, 2, 8, 9, 15, 16, 22 and 23
	With lenalidomide and dexamethasone	20mg/m^2 in cycle 1 on days 1 and 2. If tolerated, the dose should be increased on day 8 of cycle 1 to 27mg/m^2 Given on days 1, 2, 8, 9, 15 and 16 in a 28-day cycle From cycle 13, the day 8 and 9 doses are omitted	Lenalidomide: 25mg orally on days 1-21 Dexamethasone: 40mg orally or IV on days 1, 8, 15 and 22
Ixazomib (MLN9708) (Takeda Pharmaceuticals 2017)	With lenalidomide and dexamethasone	4mg on days 1, 8 and 15 in a 28-day cycle	Lenalidomide: 25mg orally on days 1-21 Dexamethasone: 40mg orally on days 1, 8, 15 and 22

Key points

- In the past two years proteasome inhibitors have risen in prominence
- Carfilzomib and ixazomib have recently been approved for the treatment of multiple myeloma
- Each agent has a different route of administration and an individual toxicity profile
- Proteasome inhibitors can be incorporated into the first line treatment of multiple myeloma alongside other drugs

Using proteasome inhibitors

When bortezomib was approved it was the only drug in its class available and was associated with several important limitations. For example, about 20-33% of patients have innate resistance to bortezomib (Fall et al 2014, Cohen et al 2016) and most others eventually develop resistance or intolerance to treatment (Fall et al 2014, Murray et al 2014). Also, a notable dose-limiting side effect of bortezomib is peripheral neuropathy (Cavaletti and Jakubowiak 2010). In the phase 2 Clinical Response and Efficacy Study of bortezomib in the Treatment of refractory myeloma (CREST) trial, 41% of participants who received the drug experienced peripheral neuropathy of any grade, and grades 3 and 4 peripheral neuropathy were reported in 8% to 15% of patients (Jagannath et al 2004). Similar incidences of peripheral neuropathy were observed in subsequent phase 3 studies of bortezomib (Richardson et al 2005, San Miguel et al 2008).

Peripheral neuropathy can be present at diagnosis, when it is often caused by an accumulation of the monoclonal protein produced by multiple myeloma cells or by comorbidities (Tariman et al 2008, Snowden et al 2011). The condition can be induced or exacerbated by neurotoxicity caused by certain anti-tumour treatments as a result of off-target, neurodegenerative effects (San Miguel et al 2006, Arastu-Kapur et al 2011). In addition to reducing patients' quality of life (Tariman et al 2008), it can lead to the need for anticancer treatment dose reductions and even to a pause in or discontinuation of therapy (Berkowitz and Walker 2012). It is therefore important to assess neuropathy before patients start treatment by asking if they have experienced numbness, discomfort or tingling sensations in their hands and feet (Tofthagen et al 2013).

The International Myeloma Foundation has developed a neurotoxicity assessment tool to support diagnosis of peripheral neuropathy (Tariman et al 2008). Patients with peripheral neuropathy at diagnosis may not be suitable for agents such as bortezomib so alternatives should be considered. First-line combinations, such as prednisone with bendamustine (Moreau et al 2013) or lenalidomide (Engelhardt et al 2010, Celgene Europe Limited 2015), can be used, and both regimens were recently approved as front-line therapy for patients ineligible for auto-SCT (Benboubker et al 2014, Celgene Europe Limited 2015).

Patients receiving bortezomib should be monitored carefully for, and educated about, signs and symptoms of neuropathy and the importance of reporting them (Tariman et al 2008). Patients may be understandably nervous that reporting signs and symptoms may compromise their anticancer treatment, but it is vital to diagnose this before permanent nerve damage occurs. Consequently, nurses need to reassure and educate patients to ensure open communication (Tariman et al 2008, Tofthagen et al 2013).

If peripheral neuropathy develops but signs and symptoms are mild and intermittent, it may be possible to continue bortezomib treatment. Patients with grade 1 peripheral neuropathy should be monitored closely, but intervention may not be required. For those with grade 2 events, the dose of bortezomib should be reduced and pharmaceutical interventions, such as gabapentin or pregabalin, administered. Patients can also be taught how to massage affected areas to relieve the symptoms. Pharmaceutical intervention may also ameliorate grade 3 neuropathy, but patients should be assessed to see if they need assistance with activities of daily living, and the potential safety implications of decreased sensation should be discussed. Therapy should be interrupted until the neuropathy has resolved. If grade 4 peripheral neuropathy occurs, treatment should be discontinued, patients should be referred for physical therapy and care should be taken that they do not place themselves in danger at home (Tariman et al 2008). As with other AEs, the risk of exacerbating existing peripheral neuropathy should be evaluated when deciding whether to retreat patients with the same agent following a good response during a previous line of therapy.

Other AEs of interest associated with bortezomib include herpes zoster virus, or shingles, reactivation, and acyclovir prophylaxis can prevent this (Pour et al 2009, Swaika et al 2012). Complete blood counts should be monitored frequently to detect haematological toxicity (Colson 2015, Janssen-Cilag International NV 2017), and thrombocytopenia, neutropenia and anaemia are common but can usually be managed with transfusions and medication (Colson 2015).

Subcutaneous administration of bortezomib may improve tolerance and lower the rate of peripheral neuropathy and other AEs (Moreau et al 2011, Arnulf et al 2012). Bortezomib is recommended for IV or subcutaneous injection (Janssen-Cilag International NV 2017) but is usually

administered subcutaneously. It must not be administered intrathecally (Janssen-Cilag International NV 2017). Treatment must be initiated and administered under the supervision of a doctor who is qualified and experienced in the use of chemotherapeutic agents. The product must also be reconstituted by a healthcare professional (Janssen-Cilag International NV 2017). A gauze pad should be used instead of an alcohol swab to avoid smearing the drug at the injection site (Colson 2015).

A recent prospective study explored the possibility of patients self-administering bortezomib at home (Lassalle et al 2015). Home administration was found to be more cost-effective than administration at an outpatient clinic and improved quality of life in 84% of participants, while 98% preferred self-administering the drug at home (Lassalle et al 2015). If self-administration becomes more common, nurses are likely to play a central role in advising and supervising patients who adopt this approach; for example it will be important to advise patients that erythema at the injection site may occur (Ng et al 2015). If injection-site reactions to subcutaneous bortezomib become a problem, a switch to IV bortezomib or a less concentrated solution of subcutaneous bortezomib (1mg/mL instead of 2.5mg/mL) is recommended (Janssen-Cilag International NV 2017). Cool compresses, corticosteroids and antihistamines may also help alleviate symptoms (Kurtin et al 2012).

In clinical studies of carfilzomib, specific AEs of interest included cardiac failure (7% of patients), dyspnoea (30% of patients), hypertension (20% of patients), thrombocytopenia (40% of patients) and hepatic failure (<1% of patients) (Amgen 2017). Peripheral neuropathy is less common with carfilzomib than with bortezomib, and data suggest that unlike bortezomib, carfilzomib treatment may not exacerbate the condition (Dimopoulos et al 2016, Bringhen et al 2017).

For patients receiving carfilzomib, routine assessments include a complete blood count including platelets, evaluation of venous thromboembolism risk and monitoring of liver enzymes (Colson 2015, Amgen 2017). Thromboprophylaxis is also recommended (Amgen 2017). Dyspnoea, although common, is usually low grade and transient (Bringhen et al 2017). If breathlessness becomes distressing, nurses can help by reassuring patients, teaching breathing control techniques, and working with patients and their carers to identify factors that alleviate or worsen the condition (Bredin et al 1999). Although rare, cardiac events have been reported in patients receiving carfilzomib so caution should be used in those with pre-existing cardiac conditions or those who have previously received cardiotoxic agents. Given that people with multiple myeloma are often older, and the disease can affect heart function, such cases are not uncommon (Kistler et al 2012). In these circumstances, nurses should work with doctors to ensure patients are thoroughly assessed at baseline and closely monitored during treatment (Bringhen et al 2017). In the case of bortezomib, antiviral prophylaxis should be considered in patients treated with carfilzomib although the risk of herpes zoster reactivation following treatment is unknown (Amgen 2017).

Carfilzomib is recommended for IV injection, and treatment should be supervised by a doctor experienced in the use of anticancer therapy (Amgen 2017). Adequate hydration is necessary before the first treatment cycle, and oral and/or IV hydration should be continued as needed in subsequent cycles. All patients should be monitored for evidence of volume overload and fluid intake, adjusted to the needs of individual patients. Serum potassium levels should be monitored at least monthly (Amgen 2017).

In common with the other proteasome inhibitors, thrombocytopenia, neutropenia and herpes zoster infection are associated with ixazomib treatment, and monitoring is recommended with prophylaxis where appropriate. Peripheral neuropathy has been reported (Richardson et al 2014, Moreau et al 2016, Takeda Pharmaceuticals 2017) so patients should be monitored for signs and symptoms before and during treatment (Takeda Pharmaceuticals 2017). Ixazomib is the only proteasome inhibitor administered orally, which can reduce the effect of treatment on patients' quality of life because there is less need for hospital visits and medical appointments (Kumar et al 2017). This also carries a risk that patients will delay reporting signs and symptoms and complications (Kumar et al 2017) so patient education on the importance of communicating AEs is crucial.

In addition to the conditions described above, people with multiple myeloma are at high risk of infection, and respiratory infections have been reported with all three agents. Educating patients on the prevention and recognition of infection and the importance of seeking treatment is essential (Snowden et al 2011). Nurses and patients

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must understand the potential safety and tolerability issues associated with the use of proteasome inhibitors because awareness, and rapid and effective management of treatment-related AEs, can help maximise patient outcomes (Colson 2015). Table 3 details the 'very common' AEs that occur in ≥1 in 10 patients and that have been reported in clinical studies of bortezomib, carfilzomib and ixazomib (Amgen 2017, Janssen-Cilag International NV 2017, Takeda Pharmaceuticals 2017).

Nurses should be aware of potential drug-drug interactions with proteasome inhibitors. Although none are expected with carfilzomib (Colson 2015, Amgen 2017) patients given bortezomib in combination with potent cytochrome P450 3A4 (CYP3A4) inhibitors, for example ketoconazole or ritonavir, should be monitored closely because these agents can increase bortezomib exposure. Patients should also avoid consuming grapefruit because it is also a CYP3A4 inhibitor (Wilkes and Burton-Burke 2016, Janssen-Cilag International NV 2017). Concomitant use of bortezomib and potent CYP3A4 inducers, such as rifampicin, carbamazepine, phenytoin, phenobarbital and St John's wort, is not recommended because these agents can markedly reduce bortezomib efficacy (Janssen-Cilag International NV 2017). Green tea may also inhibit, reduce the expression of, or cause clinically relevant interactions with, substrates for CYP3A4, although there are few studies examining whether green tea affects bortezomib metabolism (Engdal and Nilsen 2009, Misaka et al 2013, Ikarashi et al 2016). Few drug-drug interactions are expected for ixazomib although co-administration with strong CYP3A inducers should be avoided (Takeda Pharmaceuticals 2017).

Recommendations for clinical practice

Throughout the patient care journey nurses need to work closely with the MDT to ensure alignment between all parties on the latest approaches to treatment. Nurses should also keep up to date with decisions made during

TABLE 3. Adverse events classified as 'very common' (≥1 in 10) in patients treated with approved proteasome inhibitors

Medical Dictionary for Regulatory Activities (MedDRA) system organ class	Bortezomib (Janssen-Cilag International NV 2017)	Carfilzomib (Amgen 2017)	Ixazomib (Takeda Pharmaceuticals 2017)
Infections and infestations		Nasopharyngitis, pneumonia, respiratory tract infection	Upper respiratory tract infection
Blood and lymphatic system disorders	Anaemia, neutropenia, thrombocytopenia	Anaemia, lymphopenia, neutropenia, thrombocytopenia	Thrombocytopenia, neutropenia
Metabolism and nutrition disorders	Decreased appetite	Decreased appetite, hyperglycaemia, hypokalaemia	
Psychiatric disorders		Insomnia	
Nervous system disorders	Dysaesthesia, neuralgia, neuropathies, peripheral sensory neuropathy	Dizziness, headache, peripheral neuropathy	Peripheral neuropathies
Vascular disorders		Hypertension	
Respiratory, thoracic and mediastinal disorders		Cough, dyspnoea	
Gastrointestinal disorders	Constipation, diarrhoea, nausea and vomiting signs and symptoms	Abdominal pain, constipation, diarrhoea, nausea, vomiting	Diarrhoea, nausea, vomiting, constipation
Skin and subcutaneous tissue disorders			Rash
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	Arthralgia, back pain, muscle spasms, pain in extremity	Back pain
Renal and urinary disorders		Increased blood creatinine	
General disorders and administration-site conditions	Asthenia, fatigue, pyrexia	Asthenia, fatigue, infusion reaction, peripheral oedema, pyrexia	Peripheral oedema

patient-management meetings and the effect of these on the day-to-day care of patients. Collaboration with the MDT may be enhanced using agreed checklists, outlining treatment pathways to follow at each disease stage, or monitoring for, identifying and managing treatment-related AEs. Nurses should determine whether such checklists exist in their departments and adopt them as required, remaining vigilant for updates.

Time needs to be set aside to provide nurses with the appropriate education on all aspects of the management of people with multiple myeloma. Several studies have shown that knowledge of peripheral neuropathy among oncology nurses is suboptimal (Binner et al 2011, Smith et al 2014). Coordinated distribution of practice guidelines targeted at nurses, such as the peripheral neuropathy assessment tool, could improve awareness of best practice, and initiatives such as local myeloma learning programmes may be useful. Two examples of local educational programmes are the UK Myeloma Nurses Learning Programme (Myeloma UK 2016) and the Haematology Nurses and Healthcare Professionals Group Multiple Myeloma Learning Programme (HNHCP 2017). The UK programme consists of an accredited e-learning course with self-assessment modules, and covers the entire disease pathway from diagnosis to treatment and management of complications. Challenging case studies are presented alongside guides to having discussions with patients about their disease.

The HNHCP programme provides a similarly comprehensive overview of multiple myeloma with recommendations for patient management in clinical practice. Following successful development of such programmes, educational material could be shared across Europe through the European Higher Education Area scheme to ensure that all nurses receive thorough training on the management of patients with this complex disease (Satu et al 2013). Such materials would benefit from translation so that nurses can review them in their own language.

Conclusion

The management of people with multiple myeloma is complicated by the relapsing nature of the disease, its associated psychological effects, the number of different treatments and combinations that are available and the changing course of the disease following the emergence of new treatments. Nurses play a critical role during diagnosis and the early stages of the disease when they can provide much-needed patient support and education. This role continues throughout the course of the disease expanding to include supporting communication between patients and the wider care team, particularly regarding treatment choices and potential treatment complications and how to prevent or manage them, and management of the day-to-day activities at outpatient clinics. Nurses have an important role in strengthening patients' ability to self-manage their signs and symptoms, and to adhere to their anti-tumour and supportive medications. This will help improve outcomes and empower patients to take a more proactive role in the management of their condition.

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