Palliative Care Rounds

Palliative Care in Patients With Multiple Myeloma

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Key Words

Palliative care, multiple myeloma, symptom management, goals of care, advance care planning, psychosocial support

Introduction

Significant advances in the treatment of multiple myeloma (MM) over the past two decades have given rise to an increasing number of patients living with the disease for longer periods.[1] Although MM remains incurable, the five-year relative overall survival has risen from nearly 30% in the early 1990s to 40% in the early 2000s because of new treatment modalities.[2] As patients live longer, there is an impetus to place quality of life at the core of its management. Palliative care (PC) is an interdisciplinary mode of treatment aimed at relieving all aspects of suffering—physical, psychological, social, and spiritual—and promoting the most optimal quality of life for patients and their caregivers.[3] This article details the role of PC in patients with symptomatic MM using a case followed by a review of related literature. Specifically, the rationale, components, and timing of PC are discussed.

Case Description

A 49-year-old woman was hospitalized for a five-month history of headaches, mainly at the back of her head, associated with dizziness, generalized weakness, and appetite loss. Table 1 shows pertinent test results. She was diagnosed with symptomatic IgG kappa multiple myeloma, received two treatments of bortezomib and dexamethasone, and was discharged with diminished pain. At the patient's first visit, her primary oncologist continued bortezomib and dexamethasone. A social worker at the same visit provided disease- and treatment-related information and addressed financial concerns. The patient was a single mother with three young children.

Six months after diagnosis of MM, the patient developed treatment-related symptoms: neuropathy in her hands, nausea, fatigue, and insomnia. She was referred to the outpatient PC service for management of these symptoms, plus pain inadequately controlled by short-acting opioids. A combination of long- and short-acting opioids, plus gabapentin, provided better control of both her persistent head and neck pain, as well as peripheral neuropathy. The PC providers also conducted advance care planning discussions, which led to completion of advance directives. In this time frame, lenalidomide was added to her regimen in light of persistent anemia.

One year after diagnosis, elotuzumab was added after she developed new bone lesions. A month after, she was noted to have stable disease and subsequently underwent treatment with high-dose melphalan followed by autologous hematopoietic cell transplantation. She responded well to this therapy, pain and energy level improved, and she was placed on maintenance therapy with lenalidomide.

Two years after diagnosis, disease relapse was noted with an enlarged lesion in her humerus and increased protein concentration. Drug therapy was changed to daratumumab, bortezomib, and dexamethasone. She underwent resection of a right humerus lesion and shoulder arthroplasty, which resulted in marked pain relief. A few months after, two new scalp lesions were found and treated with radiotherapy. Lenalidomide was added back to her regimen.

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Three years after diagnosis, the patient complained of pain from new rib lesions. She completed yet another course of radiotherapy, and therapy was switched to carfilzomib, pomalidomide, and dexamethasone. PC continued to manage pain, as well as nausea from the new regimen. A few months after, treatment was replaced with cyclophosphamide, bortezomib, dexamethasone, and thalidomide as new lesions appeared in her pelvis and calvarium. Despite all these lesions and changes in therapy, she remained ambulatory and functional.

Four years after diagnosis, the patient remained on cyclophosphamide, bortezomib, dexamethasone, and thalidomide with no new bone lesions. PC continued to manage her symptoms, as well as provide psychosocial support.

Table 1
Pertinent Findings on Initial Laboratory and Radiologic Evaluation

CT head	8.1 cm × 6.5 cm × 6 cm mass in central skull, and lytic lesions in the calvarium and cervical spine
MRI brain	Skull bass mass destroying the clivus and extending to the paranasal sinus and nasal airway
Skeletal survey	Lytic lesions in the skull, both femurs, and both clavicles
Hemoglobin	8.4 g/dL (12.0 to 15.5 g/dL)
Calcium	14.7 mg/dL (8.5 to 10.5 mg/dL)
Gamma globulin (serum protein electrophoresis)	4 g/dL (0.7 to 1.6 g/dL)
IgG	4837 mg/dL (700 to 1600 mg/dL)
Immunofixation serum profile	IgG kappa monoclonal protein
Bone marrow biopsy	22% plasma cells
Nasal endoscopy with biopsy of parapharyngeal mass	Plasma cells

Comment

Key Features of Multiple Myeloma

MM is the second most common hematologic cancer after non-Hodgkin lymphoma.[4,5] Its annual worldwide incidence is 3.29 to 4.82 per 100,000 individuals and accounts for about 13,000 annual deaths in the U.S. and over 20,000 in Europe.[5–7] Older adults (i.e., median age at diagnosis of 69 years) and African Americans are more likely affected.[7,8] Although MM's exact mechanism is unknown, it is thought that progression from monoclonal gammopathy of unknown significance to MM occurs via specific gene mutations.[9] Furthermore, neoplastic plasma cells promote increased osteoclast activity and bone resorption resulting in the characteristic lytic bone lesions and hypercalcemia. Key components of the current criteria for diagnosis of symptomatic MM, as revised by the International Myeloma Working Group in 2014, include clonal bone marrow plasma cells ≥ 10% or biopsy-proven bony or extramedullary plasmacytoma, and one or more myeloma-defining events (i.e., hypercalcemia, renal insufficiency, anemia, bone lesions).[10]

MM has developed into a highly treatable, yet incurable malignancy. Owing to a multitude of breakthroughs—successful clinical trials, better understanding of its pathobiology, identification of novel targets for disease-modifying therapies, hematopoietic cell transplantation (HCT), and advances in supportive care—MM is now more akin to a chronic disease.[11–13] Its course has taken the form of a continuum of response and relapse, spanning years between newly diagnosed disease and refractoriness to all therapy. Routine monitoring with laboratory studies and surveillance for myeloma-defining events detect periods of relapsed and treatment-refractory disease.

Selecting the appropriate therapeutic approach depends on the patient's age, organ function, comorbidities, ability to perform activities of daily living, and wishes.[14] Therapy generally starts with a combination of drugs. Initial therapy is usually followed by high-dose melphalan then HCT, which has been found to significantly improve progression-free survival.[15,16] Maintenance therapy follows and continued until disease relapse. Drugs for MM belong to different classes: proteasome inhibitors (e.g., bortezomib, carfilzomib, ixazomib), immunomodulatory drugs (e.g., thalidomide, lenalidomide, pomalidomide), corticosteroids (e.g., dexamethasone), alkylators (e.g., cyclophosphamide, melphalan), and monoclonal antibodies (e.g., daratumumab, elotuzumab). An example of a frequently utilized combination for either newly diagnosed or relapsed disease is bortezomib-lenalidomide-dexamethasone.

One of MM's primary clinical findings is bone disease. Often highly disabling, bone disease leads to pain, pathologic fractures, spinal cord compression, and hypercalcemia.[17] Another common finding is peripheral neuropathy, which can be caused by the disease itself or by treatment with specific agents, such as thalidomide and bortezomib.[14] Renal failure arises from a myriad of factors, namely light chain cast nephropathy, hypercalcemia, hyperuricemia, dehydration, infections, use of nephrotoxic drugs, and use of intravenous contrast for CT scans.[14] Myelosuppression is a frequent finding resulting from MM itself or chemotherapy.[14] Patients are inherently at risk for venous thromboembolism owing to multiple factors: patient-related (i.e., advanced age, immobility, comorbidities, presence of central venous catheter), myeloma-related (i.e., disease burden, hyperviscosity), and treatment-related (i.e., immunomodulatory drugs combined with high-dose steroids, concomitant use of erythropoietin).[18,19] Patients develop an increased risk for infections, especially during active disease or treatment with high-dose steroids and myelotoxic agents.[20]

The symptom burden experienced by patients is quite profound because of the disease's incurable nature and cumulative toxicities from multiple lines of treatment.[21] In a systematic review of 36 studies that used validated self-report instruments for determining symptom prevalence, Ramsenthaler identified fatigue, constipation, pain, and tingling in hands and feet as the most prevalent symptoms in at least 50% of participants.[22] Other key symptoms mentioned in the study were appetite loss, diarrhea, drowsiness, dizziness, breathlessness, anxiety, sleep problems, depression, mouth problems, and nausea. Aside from symptoms, the study revealed the top quality of life problems faced by patients: decreased physical, cognitive, role, social, and emotional functioning.

Ramsenthaler published another report on symptoms and quality of life concerns, this time a multicenter study involving 557 patients in various phases of MM.[23] The investigators classified patients into three phases: 1) newly diagnosed (i.e., pretreatment or undergoing first-line treatment); 2) treatment-free interval (i.e., stable disease with no evidence of disease progression); and 3) relapsed/progressive disease (i.e., second-line therapy or above or progression on treatment). The most prevalent symptoms were pain, fatigue, breathlessness, difficulty remembering things, tingling in hands and feet, and poor mobility. Most burdensome quality of life concerns included "problems with carrying out usual activities," "worrying that the illness might get worse," and "not having enough information about what might happen in the future." Broken down by disease phase, patients with relapsed/progressive disease had the highest symptom burden and quality of life concerns, followed by patients with newly diagnosed disease. Symptom scores tended to be higher in patients receiving treatment.

Although it is clear that MM patients undergoing active treatment cope with a multitude of physical and psychosocial challenges, those with stable disease were found to bear their own struggles. Boland studied the symptom burden and quality of life issues of 32 patients with chronic, stable MM.[24] Parallel to studies mentioned previously, pain and fatigue were chiefly reported. Predominant quality of life concerns echoed those mentioned by Ramsenthaler and related to diminished physical and social functioning. Highest concerns related to loss of independence, disease progression, and shortening of lives with partners. Monterosso studied a similar cohort, those "living with, through, and beyond a diagnosis of myeloma," to determine the unmet needs of post-treatment patients.[25] Seven themes emerged from the qualitative study: information needs, experience with health care professionals, coping with side effects, communicating with family and friends, dealing with emotions, support needs, and living with the chronicity of myeloma. Same with Boland's findings, participants worried about living with an incurable disease and the inevitability of relapse.

Palliative Care Opportunities

Multiple opportunities exist for PC professionals in the care of MM patients (see Table 2). It is vital to distinguish PC from hospice at this point. In the U.S., hospice is a model of care explicitly intended for patients suffering from any life-limiting illness whose prognosis is six months or less.[26] On the other hand, patients can benefit from PC in all stages of a serious illness—shortly after diagnosis, while undergoing life-prolonging therapies, and toward life's end.

PC entails optimally assessing and managing symptoms arising from both MM and its host of treatment alternatives. Apart from bringing relief, an implication of effective symptom management is allowing patients to continue with the treatment course and preventing premature discontinuation due to adverse reaction.[1] In addition, a qualitative study to understand the role of palliative care clinicians in managing advanced cancers showed that symptom management allows providers to demonstrate their expertise and build rapport with patients.[27]

PC offers psychosocial support as patients confront various quality of life concerns bred by serious illness. The incurable nature of MM often proves to be an immense psychological burden. Even during the stable phase, MM has grown to be a unique syndrome needing coordinated management and care from different disciplines. In addition, family caregivers have been shown to be as psychologically saddled as patients, similarly burdened by the uncertainty of dealing with an unpredictable disease process.[28] Apart from clinicians, other members of a PC team, like social workers and chaplains, can assist patients and their caregivers in coping, accepting, and planning for each of MM's phases. For instance, the team can support older adults in overcoming functional impairments and obtaining resources necessary to thrive.

PC clinicians can act as a bridge between patients and their oncologists. Back describes this role as "interpreting the oncologist for the patient and patient for the oncologist."[27] PC providers are uniquely positioned to acquire information from oncologists that can be relayed to patients in a manner that is better understood and tolerated. Conversely, feedback of patients' insights and perceptions can be relayed by PC providers to their oncologists.

An important thrust of PC is facilitating advance care planning, which typically consists of reviewing goals of care, discussing end-of-life care preferences, and accomplishing advance directives. The latter entails completing a living will and designating a health

Table 2
Palliative Care Opportunities in Multiple Myeloma

Opportunity	Specific Components
1. Symptom assessment and management	• Fatigue • Constipation • Pain • Tingling in hands and feet • Appetite loss • Cough • Diarrhea • Drowsiness • Dizziness • Breathlessness • Anxiety • Sleep problems • Depression • Mouth problems • Nausea
2. Psychosocial support	• Addressing concerns related to decreased functioning in multiple levels (i.e., physical, cognitive, and social) • Addressing emotional concerns (i.e., anxiety about disease relapse and progression) • Assisting with social support and communication • Assisting with coping, accepting, and planning • Addressing caregiver concerns
3. Bridge between patient and oncologist	• Addressing information needs • Enhancing patients' and other providers' experience
4. Advance care planning	• Goals of care discussion • Completion of advance directives (i.e., living will, health care power of attorney) • End-of-life care discussion

care power-of-attorney. At the point where the disease becomes refractory to all therapies, advance care planning may need to center on transitioning to hospice care and clarifying end-of-life care preferences.

Timing of Palliative Care

Numerous studies have highlighted ongoing disease- and treatment-related problems from diagnosis of MM to its progression. In addition, current opinion favors continuous treatment to the point where the disease is refractory to any therapy. This approach implies years of dealing with drug side effects. The authors, therefore, believe that PC has a place in all phases of MM. The authors further recommend that PC be integrated as early in the MM continuum as possible. Several studies underscore the value of early PC involvement in patients suffering from malignancies, particularly solid tumors.[29–31] To the authors' knowledge, there has only been one such study focused on MM. Porta-Sales described the outcome of 67 patients referred to a PC clinic.[32] Median time from diagnosis to initial consultation was 355 days. The study found a significantly lower proportion of patients reporting moderate-to-severe pain, pain interfered less with general activity, sleep, and mood, and fewer patients reporting depression.

PC interventions are often integrated late into the care of patients with hematologic malignancies. Reasons cited for late involvement included unrealistic expectations from both patients and physicians, unclear definition of what represents advanced disease, unpredictable disease course, sudden transition from stable to late-stage disease, and misperception that PC is tantamount to end-of-life care.[33–35] Early involvement allows patients to understand the various roles the PC team will have in their care and facilitates rapport and trust building. Similarly, the PC team becomes thoroughly acquainted with patients and their caregivers, which may ease sensitive quality of life and goals of care discussions and help develop an individualized, patient-centered care plan. Social workers, chaplains, and nurses can address psychosocial concerns, including social isolation, financial stress, spiritual distress, and caregiver uncertainty. With early integration, both patient and oncologist gain a team that will follow through and assist in coping with each phase of the disease. Eventually, the PC team serves as the primary resource when the ultimate transition occurs, from seeking further disease-directed treatment to focusing on comfort and subsequent end-of-life care.

Case Resolution

The patient in the case has been dealing with MM for four years. She has endured a difficult course fluctuating from response to relapse to treatment-refractory to stable disease. She has both benefited from a broad array of disease-directed therapy (i.e., an assortment of drugs, HCT, multiple bouts of radiotherapy, and shoulder surgery) and suffered their adverse effects (i.e., fatigue, nausea, neuropathy). Pain in different body regions has been a constant since disease discovery. She has been burdened financially, has not been able to work since diagnosis, and has had to raise her children in the midst of illness. The case illustrates the complexity of caring for MM patients. The old adage of taking a village to raise a child holds true for these patients, as it often takes a team of medical oncologists, radiation oncologists, PC providers, nurses, and social workers, to provide optimal care. Oftentimes, expertise from other fields (e.g., Nephrology, Orthopedics, Psychiatry, Anesthesia Pain Management, etc.) needs to be engaged. In terms of timing, PC became involved six months after diagnosis. Although this time frame was earlier than the median time of consultation from diagnosis in Porta-Sales' study, the patient could have benefited from earlier involvement for expert symptom management and psychosocial support.

Summary

As advances in medicine allow patients to live longer with treatable but incurable MM, PC provides an extra layer of support while dealing with symptoms and quality of life concerns arising from both the disease and its treatment. Integrating PC into oncologic care offers opportunities for expert symptom assessment and management, psychosocial support, advance care planning, and bridging patients and oncologists. Although the authors advocate for prompt PC integration, further studies should continue to examine the benefits of early involvement.

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