Review Article

Palliative Care in Musculoskeletal Oncology

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ABSTRACT

Patients in advanced stages of illness trajectories with local and widespread musculoskeletal incurable malignancies, either treatment naive or having recurrence are referred to the palliative care clinic to relieve various disease-related symptoms and to improve the quality of life. Palliative care is a specialized medicine that offers treatment to the disease-specific symptoms, places emphasis on the psychosocial and spiritual aspects of life and help the patients and their family to cope with advance stage cancer in a stronger and reasonable way. The overall outcome of musculoskeletal malignancies has improved with the advent of multidisciplinary management. Even then these tumors do relapse and leads to organ failures and disease-specific deaths in children and young adults in productive age group thus requiring an integrated approach to improve the supportive/palliative care needs in end-stage disease. In this article, we would like to discuss the spectrum of presentation of advanced musculoskeletal malignancies, skeletal metastasis, and their management.

Key words: Bone tumors, Musculoskeletal oncology, Palliative care

INTRODUCTION

"Best supportive care"/end of life care is the care that helps all those with advanced, progressive, incurable illness to live as well as possible until they die. It enables the supportive and palliative care needs of both patient and family to be identified and met throughout the last phase of life and into bereavement. It includes management of pain and other symptoms and provision of psychological, social, spiritual, and practical support.[1] Patients suffering from malignant musculoskeletal tumors with widespread metastatic disease, where curative treatment is not possible with any available modality of treatment needs palliative care. Bone and soft tissue sarcomas are known to have moderate to high risk of developing distant metastasis before the initiation or during the course treatment. Approximately, 20–25% of osteosarcoma presents with lung metastasis and about 40% are known to develop distant metastasis at later stages.[2] Even though overall survival for chondrosarcoma is reasonable (70% at 5 years), few subtypes such as mesenchymal and dedifferentiated subtypes have dismal prognosis.[3] Ewing sarcoma is a systemic disease, which is also associated with high rates of systemic failures either at presentation, during, or immediately after the treatment completion. Similarly, soft tissue sarcomas are also known to disseminate leading to end-stage disease in about 50–60% of all diagnosed cases.[4] Despite advances in local control, adjuvant chemotherapy and radiotherapy, metastatic relapse after an initial clinical remission remains a significant clinical problem with 5-year survival for nonmetastasis bone and

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soft tissue sarcomas ranging from 50 to 75% with further significant drop for metastatic disease.[5] These aggressive bone and soft tissue sarcomas mainly affect adolescent and adults in their productive period of life and affect them physically, psychologically, and spiritually requiring a holistic approach to address their needs.[6]

Apart from primary bone sarcomas, skeletal system is a common site for disease dissemination from visceral malignancies such as lung, prostate, breast, thyroid, and kidney. Although there is availability of diagnostic tools, systemic and local therapy, the burden of primary malignancies and prevalence of skeletal metastasis has increased many folds. More than 50% of lung cancer, breast cancer, and prostate cancer patients develop skeletal-related events (SRE) at diagnosis or during the treatment. SRE can present with pain, pathological fracture, or with spinal cord compression (with or without neurological deficits) causing major morbidities and compromises the quality of life [Figure 1].[7] It poses an incredible challenge for palliative medicine to deal with all these end-stage disease patients who present at varied age groups with diverse social, economical, and spiritual agony. The treatment has to be tailored to the individual patient need for better quality of life. The present article discusses the various presentations of terminally ill patients with musculoskeletal primary and secondary malignancies and related treatment and rehabilitation.

Pain management in primary and metastatic musculoskeletal tumors

Pain arising from the primary site of the tumor or the site of skeletal metastasis of musculoskeletal sarcoma or other carcinomas is one of the most important causes of distress and discomfort for palliative care patient [Table 1]. Effective pain management makes the patients comply with the treatment protocol. The treatment offered should be individualized according to the disease status, existing comorbidities, and the intensity and severity of symptoms. The treatment approach should be least invasive, safe, fast acting, effective, and sustainable.

Genesis of pain

Skeletal pain occurs due to loss of normal bony strength by destruction of bony architecture by tumor cells. This can occur at the site of the primary tumor or at metastasis in other bones. Skeletal system is a very common site for metastasis in primary musculoskeletal sarcomas as well as from other malignancies. 37–70% of all cancer patients develop skeletal metastasis at some stage of their life.[8] Apart from metastasis in appendicular leading to pathological fractures, axial skeleton metastasis is associated with pathological fractures and spinal cord compression leading to paraparesis or distal neural deficits.[9] Visual analog scale is the most common scale used for objective pain measurement[10] [Figure 2].

Measures for pain control

Achieving an effective pain control in the end stage disease is an art, which requires a multipronged approach [Table 2].[11] This involves a detailed explanation and counseling of the patients and the attendants regarding the disease process and prognosis, alteration of the pathological process, addition of local therapy to halt or retard disease process, interruption of the pain producing pathways, lifestyle modification, and use of orthotics and prosthesis and sometime immobilization. Pain can be dealt with nonpharmacological and pharmacological approaches. Brad *et al.* in their study showed that music could reduce anxiety, pain, and improve mood and quality of life.[12] Jane *et al.* concluded that massage therapy could reduce the intensity of pain, improve quality of sleep and mood.[13] The pharmacological approaches available are medication, nerve blocks, radiofrequency ablation (RFA), radiotherapy, chemotherapy, embolization, cryoablation, high frequency focused ultrasound, vertebroplasty, and kyphoplasty.[14] The basic and initial approach that is used is 'medication by the mouth, by the clock and the by the WHO ladder.[15]

Bone strengthening agents such as bisphosphonates and newer agents such as monoclonal antibody to receptor activator of nuclear factor-kappa-B ligand (RANKL) (denosumab) are proven to reduce

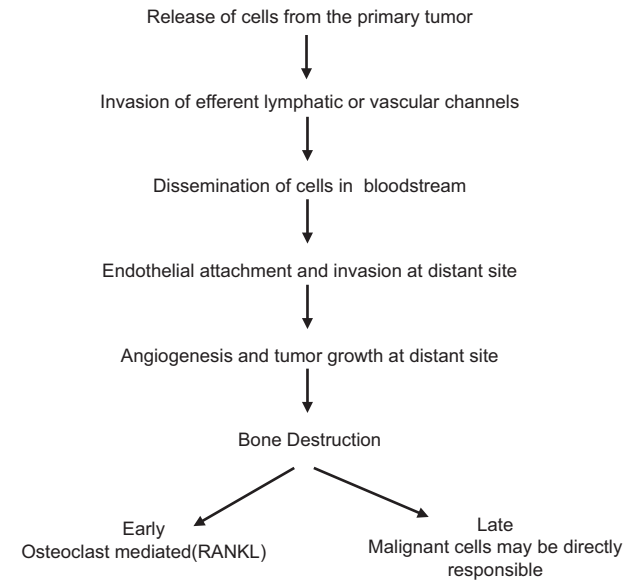

Figure 1: Mechanism of metastasis and bone destruction

Table 1: Acute and chronic pain syndromes

Acute pain causes	Chronic pain causes
Due to procedures and therapies	Multifocal or generalized pain (focal metastases or marrow expansion)
Bone marrow biopsy	Base of skull metastases
Lumbar puncture	Vertebral syndromes
After strontium-89 therapy of metastatic bone therapy	Pain syndromes of the bony pelvis and hip
	Tumor invasion of joint and/or soft tissue
	Paraneoplastic pain syndromes
	Hypertrophic osteoarthropathy
	Malignant pelvic and perineal pain
	Painful osteonecrosis
	Radiation-induced or corticosteroid-induced necrosis of femoral or humeral head
	Osteoradionecrosis of other bones
	Painful lymphoedema
	Due to radiation therapy
	Radiation-induced chronic pelvic pain
Acute postoperative pain	Neuropathic pain syndromes
Tumor embolization	Painful peripheral mononeuropathies
Pain associated with bone marrow transplantation	Painful polyneuropathies
Pain from intravenous or intra-arterial infusion	Plexopathy
Intraperitoneal chemotherapy	Radiculopathy
Headache due to intrathecal chemotherapy	Epidural spinal cord compression
Painful oropharyngeal mucositis	
Painful peripheral neuropathy	
Diffuse bone or muscle pain from colony-stimulating factors or chemotherapies	
Fluorouracil-induced angina	
Acute pain associated with radiation therapy	
Due to the neoplasm	
Vertebral collapse and other pathological fractures	
Acute obstruction of hollow viscus (e.g., bowel, ureter, bladder outlet)	
Hemorrhage into tumor	
Acute pain associated with infection	
Myalgia and arthralgia associated with sepsis	
Pain associated with superficial wounds or abscesses	

the SRE in both lytic and blastic bone metastasis.[16,17] They prevent osteolysis, hypercalcemia, microfractures, and vertebral collapse thus reducing the bone pain and improving the patient quality of life. Zolendronic acid is the most potent and commonly used bisphosphonates with associated side effects such as anemia, gastrointestinal symptoms (e.g. nausea, vomiting, diarrhea, or constipation), fatigue, fever, weakness, arthralgia, myalgia, and less commonly, hypocalcaemia. Serious complication associated with amino-bisphosphonates is osteonecrosis of jaw, a dental evaluation, and preemptive dental treatment are mandatory before starting treatment. Bisphosphonates require dose adjustment in patients with renal insufficiency. Calcium and Vitamin D supplementation helps to prevent hypocalcemia.[16] Denosumab, a fully human monoclonal antibody to RANKL, is a more potent inhibitor of osteoclastogenesis and bone resorption. It has been approved for the treatment of postmenopausal osteoporosis as well as bone metastases from solid tumors and multiple myeloma. Denosumab was reported superior to zoledronic acid in preventing SRE. It is easier to administer, does not require dose adjustments for renal insufficiency and not associated acute reactions. The main drawback of this drug is its high cost.[17] The effects of these drugs are well-documented in metastatic carcinomas.

Radiotherapy is a noninvasive and one of the most effective modalities for the management of pain in palliative setting. For palliative pain relief, single fraction (8–10 Gy) and multifraction (30 Gy in 10 fraction) radiotherapy have shown similar efficacy, the rate of reradiation and pathological fracture are more associated with single-fraction treatment.[18,19] Koontz *et al*. treated 21 cases of metastatic Ewing sarcoma with palliative radiotherapy (Median dose-30 Gy) and showed complete response to symptoms in 55% and partial response at 29% of sites.[20]

Numerous minimally invasive procedures are available if the radiation fails to achieve desired pain control. RFA, cryoablation, high frequency focused ultrasound,

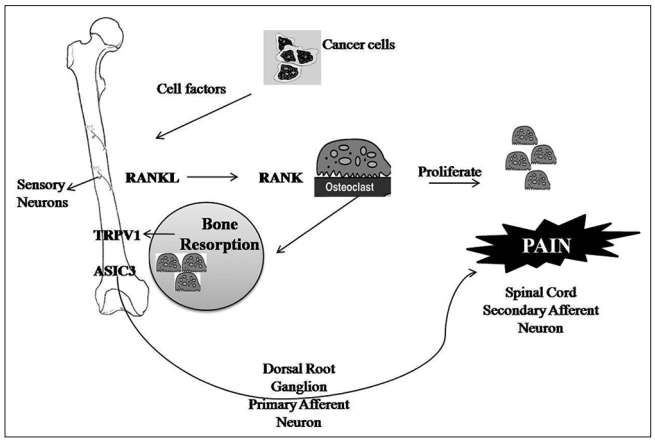

Figure 2: Mechanism of musculoskeletal pain: Neoplastic cells secrete diverse cell factors to promote proliferation and stimulate osteoclastic bone resorption via receptor activator of nuclear factor-kappa-B ligand/receptor activator of nuclear factor-kappa-B pathway in osteoblasts and osteoclasts. Osteoclasts create an acidic microenvironment by secreting H^+ ions causing dissolution of bone minerals causing structural disintegration which may lead to pathological fracture. The acidic microenvironment excites sensory neurons in the bone by the activation of acid-sensing nociceptors transient receptor potential vanilloid 1 and acid-sensing ion channel 3, transducing noxious signals via the dorsal root ganglion (primary afferent neuron) and then the spinal cord (secondary afferent neuron) and causes the sensation of pain

Table 2: Nonpharmacologic and pharmacologic measures for pain control

Nonpharmacological	Pharmacological
Music	Opioids
Massage therapy	Morphine
Lifestyle modification	Nonopioid
Immobilisation	Acetaminophen
Rehabilitative approaches (bracing)	Nonsteroidal anti-inflammatory drugs
Psychologic approaches (cognitive therapy)	Adjuvant
	Corticosteroids
	Calcitonin
	Topical (capsaicin, phenoxybenzamine)
	Drugs for bone pain
	Bisphosphonates (e.g., zoledronic acid and ibandronic acid)
	Radiopharmaceuticals (e.g., strontium-89 and samarium-153)

image-guided percutaneous cementing and microwaves are proven to be effective in reducing pain and increasing bone strength.[21] In RFA, an alternative current is applied at the target tissue with the help of interstitial electrodes, the current produces oscillating tissue ions which results in the frictional heat at target tissue. The disadvantages include increased tissue impedance resulting in limited application of additional current, skin burns, and thermal injury to surrounding vital structures.[22] Callstrom *et al.* reported good pain relief with cryoablation in skeletal lesions with advantage over RFA in terms of pain experienced during and post procedure and better visualization of ablation margin avoiding injury to surrounding tissue.[23] Image-guided percutaneous cement installation can prevent impending pathological fracture and the pain, mainly useful in spine and weight bearing bones. Thermal heat generated during polymerization of cement damages nerve endings and reduces pain and because of its mechanical property, it gives structural support to weak bone.[24] Combination of RFA and cementoplasty has shown a significant decrease in pain in lytic bone lesions with decrease in mean visual analog scale score of 8.5–3.5[25] [Figure 3]. High-frequency focused ultrasound is done under magnetic resonance imaging where rapid heat is generated within the tissue (temperature of 65–85°C) and destroy the tissue by coagulation necrosis. HIFFU is contraindicated in the lesions, which are close to neurovascular bundle, spinal cord, and small superficial lesions close to skin. Recent studies have demonstrated significant pain relief as well as control of primary lesions with HIFU.[26]

Pathological fracture

Patients can present impending or complete pathological fractures which add significant morbidity. Depending on the survival and prognosis, the treatment modality can be either conservative or aggressive. The intent of the procedure would always be palliative. The main goal of the procedure is early mobilization so that patient is capable of independent self-care. This is achieved by structurally replacing the damaged host bone by metallic endoprosthesis or by fixing the fracture with adequate implants and bone cement [Figure 4]. The main aim is to have a reconstruction, which should outlive the patient's expected lifespan.[27] Plaster immobilization or functional brace is the age-old basic method of fracture stabilization; it can be a temporary makeshift and in some cases can be continued as the definitive management if life expectancy is extremely poor. Impending pathological fractures should be graded as per Mirels' scoring system ([Table 3] Mirels' scoring system for impending pathologic fractures),[28] which guides a surgeon to take a decision for prophylactic fixation or to treat it with conservative methods.[27] Immediate stabilization and early mobilization can be accomplished with preferably intramedullary stabilization (weight sharing devices) and filling of the defect with bone cement. This kind of construct would give immediate stability instead of depending on the hosts' body response and bone to heal and that too in a setting where the healthy bone has been replaced by metastatic deposits. Peritrochanteric fractures in lower limbs and lesions with large bone defect are preferably treated with replacement arthroplasty. Patients with minimal vertebral collapse (>50% of vertebral height)

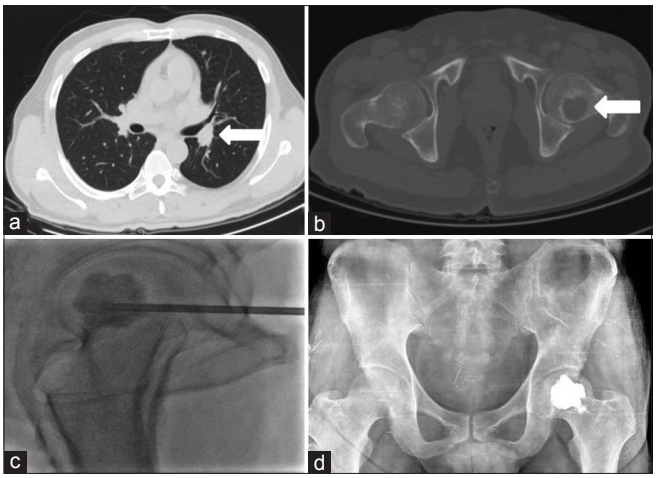

Figure 3: (a) Computed tomography image showing carcinoma of the lung. (b) Computed tomography image showing skeletal metastasis in the proximal femur with intact cortex all around. (c) Image showing percutaneous cement injection after radiofrequency ablation. (d) Radiograph showing cementoplasty of the proximal femur defect

Figure 4: (a) Bone scan showing extensive skeletal metastasis of a breast carcinoma patient. (b) Radiograph showing pathological fracture of the proximal femur. (c) Radiograph showing replacement of diseased and fractured proximal femur with megaprosthesis for better quality of life

Table 3: Mirels' scoring system for impending pathologic fractures

Location	(1) Upper extremity	(2) Lower extremity	(3) Intertrochanteric
Radiographic appearance	Blastic	Mixed	Lytic
Size[a]	<1/3	1/3-2/3	>2/3
Pain	Mild	Moderate	Functional[b]

[a]Size is determined as a fraction of the cortical thickness; [b]Functional pain is defined as severe pain or pain aggravated by limb function

Score	Fracture risk (%)	Recommendation
≥9	33-100	Prophylactic fixation is recommended
8	15	Clinical judgment should be used
≤7	<4	Observation and radiation therapy can be used

with no neurological deficit are treated with bracing and radiotherapy. Unstable spine, multiple vertebral compression, or patients with neurological deficits are managed by spinal decompression with instrumentation [Figure 5]. Bone cement can be used in vertebroplasty and acetabuloplasty in contained vertebral collapse and periacetabular metastasis, respectively. This will palliate both pain, prevent the ongoing postural deformity, and will enhance the mobilization of these patients.[29,30] Amputation as a palliative procedure has been well-documented for advanced bone and soft tissue tumors. Pain alone should not be a deciding factor for major amputations unless it involves complications such as fracture, hemorrhage, and/or fungation. According to Malawer *et al*.,[31] the indications for palliative major amputations include involvement of a proximal limb or a major joint, accompanied by intractable pain, sepsis, tumor fungation, hemorrhage, vascular thrombosis, pathologic fractures, radiation-induced necrosis, or a limb with severe functional impairment [Figure 6].

Tumor fungation

Tumor fungation generally occurs at the site of primary tumors. In aggressive bone and soft issue tumors, discrepancy between the rate of growth and the vascular supply of the feeding vessel frequently give rise to foul smelling fungating tumor mass.[32] Necrosis of the overlying epithelium makes the surface raw, resulting in bleeding, accumulation of the blood clot and resulting in secondary anaerobic infection. This poses a serious concern for the patient as well as the caregivers and the attendants. Management: Regular dressing of the wound and keeping the surrounding area clean with application of antibiotic creams; locally acting hemostatic agents will help. Patients with huge unresectable tumors with frequent intratumoral bleeding can be managed with hemostatic radiotherapy (mean dose 20 Gy).[33] Bleeding tumors in the inaccessible area such as pelvis and spine can be treated with angioembolization. Palliative limb ablative surgery may be required for large fungating and bleeding tumors in extremities.

Lymphedema

Patients presenting with lymphedema and brawny edema with glossy skin is one of the most common presentations in palliative clinic. It may be due to compression of lymphatic drainage by primary tumors, secondary to previous surgeries, postradiation or due to metastatic involvement of the draining lymph node.[15] Severe lymphedema can result in functionless limb. The main concerns are to decrease or to control the lymphedema, prevent secondary infection, prevention of pressure sores, care of dry and glossy skin and fissures. Management: Basic measures taken to prevent lymphedema are limb elevation, elastic stockings, custom

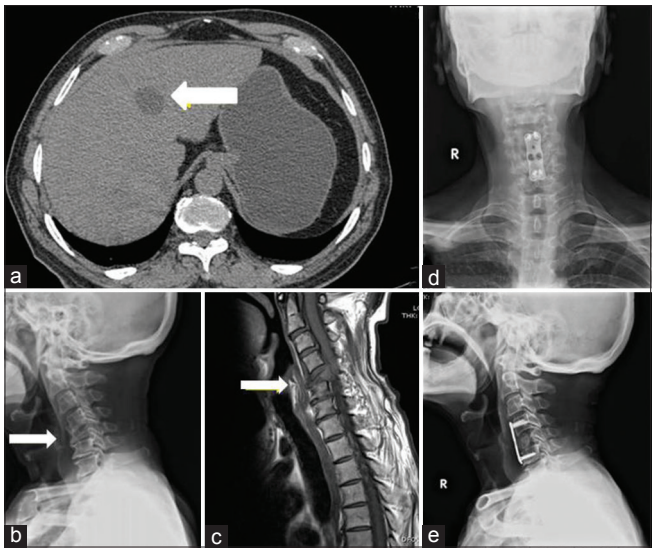

Figure 5: (a) Computed tomography image showing hepatocellular carcinoma. (b) Radiography showing collapse of the C5 secondary to metastasis from hepatocellular carcinoma. (c) Sagittal T1 magnetic resonance image showing collapse of the C5 vertebra and compression of spinal cord. (d and e) Radiographs showing anterior decompression of the spinal cord and stabilization of C5 with plate

made sleeves, gentle message, and judicious use of diuretics.[15] Patients with functionless limb due to severe lymphedema, not responding to standard treatment can be offered palliative amputation.

Gastrointestinal symptoms

Patients presenting with nausea and vomiting is not very uncommon in palliative bone and soft tissue sarcoma patients. Most commonly, it is drug induced. However, care must be taken to identify the specific receptors responsible for the symptoms as because the management is entirely receptor targeted.[34] Drugs such as morphine used as potent analgesics act on the chemoreceptor trigger zone and may produce nausea and vomiting. All these may be a deterrent in taking effective treatment. Dopamine antagonist such as haloperidol and metoclopramide provide good relief. Vomiting can be also due to stimulation of 5 HT3 receptors, most often by stretch of the gut wall, chemotherapy, and radiotherapy or due to stasis caused by obstruction.[35] Cancer patients generally are cachectic have loss of appetite due to both the disease process and cytotoxic therapy. Consequently, their intake is decreased resulting in chronic constipation. Patients taking opioid analgesics suffer from constipation as a side effect from the drug. Stool softener along with intestinal motility agents are recommended for opioid-induced constipation. Occasionally, a phosphate enema may be required for evacuating any retained fecal matter.

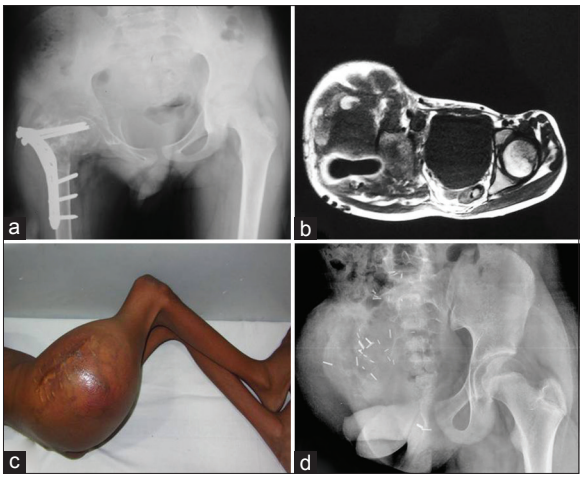

Figure 6: (a) Radiograph showing osteosarcoma of proximal femur with pathological fracture with plate *in situ* (b) T1 axial magnetic resonance image showing osteosarcoma of proximal femur with soft tissue component. (c) Clinical picture showing large swelling in the proximal femur with surgical scar. (d) Patient underwent palliative hindquarter amputation in view of extensive metastasis. Radiograph showing post hindquarter amputation status

Respiratory distress

Lung being one of the most common sites of metastasis for musculoskeletal malignancies, patients presenting in the palliative clinic with respiratory distress are quite common. Distress can be due to large pulmonary metastatic deposits leading to insufficient pulmonary parenchyma or due to the presence of large pleural effusion or pneumothorax. Plain radiography of chest, ultrasonography, and computer tomography are the most commonly used imaging modalities to diagnose and plan the treatment in these cases. Chest physiotherapy with incentive spirometer, propped up position, intermittent moist oxygen inhalation, and nebulization with salbutamol will help to improve the patient condition. Image-guided or conventional therapeutic drainage of the fluid may relieve the patients of the distress. Malignant pleural effusions have a characteristic tendency of quick refill. This situation can be managed by pleurodesis by instillation of talc in the pleural cavity or antibiotics.[15] In refractory dyspnea, low-dose opioids such as morphine and benzodiazepines relieve the distress of breathing.

Psychological care

"Breaking the Bad News" is a challenge both for the doctors and the patients and their family. This is a situation, which everybody wants to avoid. It should be prompt, based on factual information and case notes and most essentially with the empathetic bent of mind. Anxiety comes from the symptoms of the end-stage

disease and for the other family members regarding their future in his or her absence.[35] This anxiety-depression goes on in a vicious cycle and demoralizes the patient and affects the quality of life badly. Psychiatrist and the psychologist play a very vital role to make them understand the disease status and its outcome and to train them mentally and emotionally to face the situation. Regular counseling sessions can help the patients to manage their psychological distress. Screening for depression is important and small patient population will benefit from pharmacological management.

Systemic treatments

Hormonal therapies, newer receptor-specific drugs, and monoclonal antibodies have changed the treatment of metastatic carcinomas. Studies have shown significant improvement in survival and quality of life with these drugs.[36,37] Low-dose metronomic chemotherapy has evolved as a newer bullet in the treatment of advanced refractory tumors. The basic concept of metronomic chemotherapy is to use low-dose multi drugs (due to heterogenecity of tumors) over a relatively long duration of time with no extended drug-free break. It mainly targets the angiogenesis of tumors resulting hypoxia and depletion of nutrition. These have resulted in significant improvement in the quality of life and survival in advanced tumors.[38] Thus, medical oncology plays a vital role in the management of palliative cancer patients.

CONCLUSION

Palliative care, in a nutshell, is the constellation of services that improves patient-related outcomes in advanced stages of cancer. The specialized care helps the patients and their families to cope with the perils of advanced illness. When a patient is declared "Best supportive care," he or she is referred to the palliative care clinic where a holistic approach is commissioned to counsel the patients and their families, educate them and provide required evidence-based treatment to resolve the physical, psychological, and spiritual misery. Role of palliative care in bone and soft tissue sarcoma is immense because the inherently aggressive malignant tumors too often show local and distant recurrence in spite of multimodality treatment even in the best of the sarcoma treatment centers. This is the reason that from times long ago, hospice centers are operative throughout the country. Hospice centers are not just a place; it is an idea that enables patients to live well and die well. Palliative care requires the involvement of multidisciplinary approaches such as palliative medicine, Intervention radiology, radiotherapy, surgical oncology, and chemotherapy.

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Conflicts of interest

There are no conflicts of interest.

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