

Care of cancer patients with liver and bone metastases – the place of pharmaceutical care in a balanced plan, focused on the patient’s needs and goals

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Abstract

Metastatic cancer, especially in the growing population of geriatric patients, presents a big challenge to these patients, as well as to treatment teams and the entire health care system. This article describes some common medical problems faced by patients with metastases to liver and bone, and presents a diagnostic approach, and therapeutic management of various symptoms, relevant to advanced stages of the malignant disease. The article highlights the importance of patient education on various aspects of metastatic cancer, and underscores the unique position of pharmacists practicing pharmaceutical care, which is particularly beneficial in this group of patients with advanced malignancy. Also, this paper emphasizes that achieving a proper balance between managing the malignant disease and maintaining the patients’ quality of life, especially in the elderly population, should involve coordinated efforts of the oncology treatment team, primary care physicians, pharmacists, therapists and nurses, as well as patients, their families and caregivers.

Key words: patients with metastatic cancer, patient education, integrative care, pharmaceutical care, quality of life.

Introduction

In approaching difficult topics, relevant to metastatic cancer, with patients and their families or caregivers, oncology and palliative care specialists, as well as primary care physicians, who usually have an established professional relationship with these patients, may consider a few important steps. Medical teams, working together with pharmacists, who provide pharmaceutical care, as the patients progress to more advanced stages of their malignancies, can efficiently implement these steps into practice. As the initial step, it is crucial to assess the patients’ understanding of their disease, including any individual opinions about the prognosis. Depending on that, both patients and families should be informed, in a professional, clear and emphatic manner, that they are facing a serious “marathon”, related to their disease course. At the same

time, the patients, regardless of their age, need to know that the physicians, pharmacists, and other members of the treatment team will collaborate with them, and will spare no efforts to help them choose the most appropriate treatment options, to improve both the length and the quality of their lives [1]. The team approach to treating patients with the metastatic disease, including an attending primary care physician, an oncologist, a palliative care specialist, a psychologist, a pharmacist, a rehabilitation therapist, and qualified nursing staff, is definitely recommended, since these experts are instrumental in discussing a diagnosis and a possible, realistic management plan, in advanced stages of malignancy. At this point, the patients', their families' and caregivers' education and support are also crucial, in order to deliver the best possible care, to minimize suffering, and to reduce unnecessary medical costs [1, 2].

Methodology of the review process

The search that we performed was based on an Internet medical literature review, using the Medline-PubMed and Cochrane Library databases. The key words used to search the references used in the text included the following terms: metastatic cancer, liver metastases, bone metastases, advanced cancer (diagnostic work-up, skeletal complications, pharmacologic management, non-pharmacologic management, symptom management, individualized support, pharmaceutical care, adherence to treatment, patient education, quality of life (QoL), integrative and complementary therapies, patient-centered approach, healthcare costs). The search strategy was based on the above listed terms AND the use of vignettes in the Medline published studies or reviews. Upon reviewing all of the obtained publications from the performed search, we analyzed in detail the publications from the period 2010–2015. The main search timeframe was set for the last 5 years due to the recent rapid development of the diverse diagnostic and therapeutic methods in the oncology field. However, we also included some earlier publications (from 1987–1999), in order to illustrate differences between past and present modern diagnostic work-up procedures performed in patients with cancer. After we identified the most pertinent abstracts, we reviewed them to ascertain their content. The abstracts that were most focused on goals of our review were selected, and full publications were reviewed and then included as references.

Key issues in patient and family education and support in advanced stages of metastatic cancer

Depending on an individual patient's psychophysical condition, emotional stability, insight,

and general level of knowledge, 'basic teaching' on all aspects of metastatic cancer may include:

- the biology of particular malignant disease,
- diagnostic test (advantages and limitations),
- treatment options (benefits, risks, and alternatives),
- symptom management, with focus on pain control,
- management of the adverse effects of the treatment,
- emotional support for patients and their families or caregivers.

This educational sequence plays a vital role in the entire therapeutic process, and thus it should be conducted in a simple and pragmatic manner, so that it can be easily understood by patients [1, 2].

Along with a comprehensive evaluation of the extent of metastatic disease, some difficult issues need to be addressed, such as the following:

- how to set goals in metastatic disease (advanced incurable disease)?
- how extensive should the diagnostic work-up be?
- which treatment options should be explored, selected or declined?
- how does one raise the topic of palliative care or hospice?
- how does one bring up end-of-life care?

A silent stage of cancer progression

It is very unfortunate for many patients with cancer that recurrent metastatic disease, with long latency periods (years or even decades), can develop without any clinical symptoms. This phenomenon is related to cancer dormancy that represents an early, silent stage of cancer progression. Although its complexity is not fully explained, some clinical evidence exists, indicating different mechanisms of cancer dormancy, such as angiogenic dormancy, cellular dormancy (G0–G1 arrest) and immunosurveillance [3]. Also, for a treatment team, it is very challenging to identify the mechanisms of cancer dormancy in individual patients, and to determine biomarkers and potential therapeutic targets, accordingly. Recently, cellular or serum biomarkers have emerged as potential help in detection of the dormant stages of malignancy. Moreover, transcriptional profiles from dormant disseminated tumor cells can determine whether primary neoplastic lesions contain a so-called 'signature' of cancer dormancy, which can represent an important prognostic factor [4]. Hopefully, a better understanding of mechanisms leading to tumor dormancy can, in the near future, uncover innovative therapies, aimed at preventing metastases.

At the present time, in many patients' view, metastases to the liver and to the skeleton represent

particularly ominous prognostic signs, and thus it is important to elucidate the details of modern diagnostic work-up of these complications, prior to making final decisions, relevant to metastatic disease management. This should be done in a calm and competent manner, since cancer patients deserve credible, unbiased information about any diagnostic step, intervention or treatment regimen that may be considered. At this point, it is of utmost importance that the medical team members carefully listen to patients' concerns and work with them in a partnership to develop the most optimal plan, specific to each patient's individual needs. Complex medical terminology should be presented to patients in a simple way, to ensure their understanding. This open dialogue should help both patients and providers focus on constructing the care plan that is most appropriate for a given patient. In addition, with such an approach, it will be possible to avoid certain unnecessary, costly or toxic therapies that are not desired by some patients. Finally, offering to the cancer patients lifelong support, providing them with simple exercises and self-care techniques, as well as cultivating hope, should be incorporated into all conventional oncology care systems, as human priorities.

Liver metastases

The liver provides a suitable territory for metastases, because of its dual blood supply, and also due to presence of many humoral cell growth factors. The fenestrations in the sinusoidal endothelium of the liver allow malignant tumor emboli, from the blood stream, to create metastatic lesions [5].

Most liver metastases are multiple, and in majority of cancer patients they involve both hepatic lobes. These growing metastatic tumors usually vary in size, and compress adjacent liver parenchyma, causing atrophy or producing connective tissue. Large metastases may even outgrow their own blood supply, causing central necrosis of the lesion. About one half of the patients with liver metastases can manifest clinical signs of ascites or hepatomegaly, while their liver function tests may still, for a long period of time, remain unremarkable [6].

Different factors that can affect the pattern of liver metastases include:

- the patient's age and sex,
- the primary site of cancer,
- the histological type of malignancy,
- the duration of the neoplastic disease [6].

Most tumors that metastasize to the liver, e.g., breast and lung cancers, can simultaneously spread to some other sites. Only in certain tumor types, including colon carcinoma, carcinoid, and

hepatocellular carcinoma (HCC), are metastases usually confined to the liver [7].

Some focal lesions can be resected surgically, or treated via ablation techniques. Imaging tests play a vital role in the diagnosis of liver metastases, and in the assessment of the response to treatment. The identification of liver abnormalities as metastatic lesions, in many cases, can significantly influence the patient's treatment plan and prognosis. Liver metastases often appear on the imaging scans as nonspecific abnormalities [6].

In evaluation of liver metastases, the following diagnostic imaging tests are useful [8]:

- Ultrasonography (US) is widely used in the investigation of suspected liver metastases.
- Computed tomography (CT) is the imaging scan of choice for evaluating liver metastases. It also permits better assessment of the neoplastic involvement of extrahepatic tissues, including the bones, lymph nodes, bowel, and mesentery.
- Magnetic resonance imaging (MRI) allows the effective localization of hepatic and vascular neoplastic invasion, but is expensive.
- Intraoperative ultrasonography (IOUS) of the liver has the highest sensitivity for the detection of focal hepatic lesions, with 96% accuracy (versus the accuracy of transabdominal US, which is about 84%).
- Color-flow imaging has an advantage of providing additional details in the localization of abnormalities, the differentiation between blood vessels and biliary ducts, the presence of vascular invasion, occlusion, or collateral circulation, as well as vascularity of liver metastases.
- Selective hepatic angiography may demonstrate hypervascular liver metastases by showing capillary blush in involved areas, highlighting the potential response of tumors to embolization. Angiography is essential when hepatic vascular intervention is planned. However, this procedure is performed in highly specialist centers.

According to the meta-analysis, comparing US, CT, MRI, and fluorodeoxyglucose (FDG) imaging in the detection of liver metastases from colorectal, gastric, and esophageal cancers, it was concluded that FDG positron emission tomography (PET) is the most sensitive noninvasive imaging modality for the diagnosis of liver metastases [8]. However, this test is very expensive, and unavailable to the majority of patients at present.

Although imaging plays a vital role in the diagnostic work-up of liver metastases, biopsy specimens are required for accurate histological diagnosis. The diagnostic differentiation between benign (e.g., granulomatous) and malignant liver lesions is difficult, mostly due to various abnormalities or pseudolesions that mimic metastases

or coexist with them. The following abnormalities should be included in the differential diagnosis:

- focal fatty infiltration,
- scars after liver surgery,
- cystic fibrosis,
- focal nodular hyperplasia (FNH),
- atypical hemangiomas,
- hydatid liver disease (with hydatid cysts, which can be unilocular, multilocular, solid or calcified) [9].

In general, metastases cause hepatomegaly, but this is clinically evident when the disease is very advanced. Sometimes, the surface of the liver appears nodular, or its shape is altered. Since the appearance of liver metastases is nonspecific in imaging examinations, a biopsy is necessary for a definite tissue diagnosis. Percutaneous biopsy should not be undertaken if curative hepatic resection may be possible [10]. Unfortunately, the presence of multiple hepatic tumors of various sizes is quite often the result of the metastatic process. In this situation, a patient's general status and overall clinical picture will determine final decisions, regarding feasibility of any further diagnostic or therapeutic steps.

Bone metastases

Metastases from different types of primary carcinomas to the bones are common malignant tumors of the skeleton. Radiology imaging tests play an important role in the diagnosis, treatment plan, prognosis, and monitoring of bone lesions. Bone can be involved in metastases by:

- direct extension,
- retrograde venous flow, in which spread from intra-abdominal cancer involves the vertebrae,
- seeding with tumor emboli, via the blood circulation, which occurs in the red marrow.

In addition, increased intra-abdominal pressure causes blood to be diverted from the systemic vena cava system to the vertebral venous plexus, and this diversion allows the caudal and cranial flow of blood, and determines the distribution of metastatic lesions. In patients with previously confirmed neoplastic tumors, radiology imaging allows one to screen the skeleton for metastatic disease, and to determine its extent [11, 12].

Primary disease sites in bone metastasis

Among women, the breasts and lungs are the most common primary cancer sites, and about 80% of cancers that spread to bone arise in these locations, and among men, cancers of the prostate and lungs comprise 80% of the carcinomas that metastasize to bone [13]. In patients of both sexes, the remaining 20% of primary disease sites include the kidney, thyroid, gastro-intestinal tract or sites of unknown origin [13].

Bone metastases can be multiple at the time of diagnosis, and the lesions are often localized in the axial skeleton, including the vertebrae, pelvis, proximal parts of the femur, ribs, proximal part of the humerus, and skull. Some carcinomas have a tendency to spread to particular skeletal sites. For instance, about 50% of hand metastases originate from lung carcinomas, and primary tumors arising from the pelvis usually spread to the lumbosacral spine. As metastatic lesions increase in the medullary cavity, the surrounding bone is remodeled by osteoclastic or osteoblastic mechanisms. The level of bone resorption versus deposition is variable, and depends on the type and location of the tumor. The interplay in the remodeling, caused by osteoclasts and osteoblasts, determines which pattern of bone lesions: sclerotic, lytic, mixed – will dominate in radiology imaging tests [14].

Patients with bone metastases often suffer from severe pain, and may present with pathologic fractures, or with complications such as neurologic impairment, due to spinal epidural compression [14].

Diagnostic workup of metastatic bone disease includes laboratory tests such as:

- serum alkaline phosphatase (indirect marker of bone destruction),
- serum protein electrophoresis,
- urinalysis, urine protein electrophoresis,
- N-telopeptide of type II collagen (marker of bone resorption, rarely used).

Diagnostic radiology tests to evaluate bone metastases have certain advantages and limitations, which should be considered ahead of time and then explained to the patients.

The following radiology imaging studies are recommended to evaluate metastatic bone disease [15–17]:

- X-ray radiography, to initially assess the extent of a tumor and bone erosion,
- CT scanning, a more sensitive imaging modality, assessing the extent of bone destruction,
- MRI scanning, the most sensitive study for evaluation of the anatomic (intramedullary and extraosseous) extent of lesions,
- Radionuclide bone scanning (bone scintiscan), a very sensitive study for the detection of occult neoplastic lesions,
- Bone scintiscan with technetium-99m is a whole-body screening test for the assessment of bone metastases, including their biologic activity [17].

Indications for bone scintiscanning include:

- cancer staging in asymptomatic patients,
- assessment of persistent pain in the face of negative radiographic tests,
- examination of the extent of bone metastases,
- distinguishing between traumatic and pathologic fractures,

– determining the therapeutic response to metastases.

Both CT scanning and MRI are helpful in evaluating suspicious lesions, seen on the bone scintiscan [13, 15, 17]. CT scanning is also useful in guiding needle biopsy, especially in vertebral lesions. Magnetic resonance imaging is helpful in determining early lesions and the extent of local disease, which is crucial in planning a surgical procedure or radiation therapy. The MRI is expensive. Plain radiographs are rather insensitive in the detection of early or small metastatic lesions, but they can characterize larger lesions such as osteolytic, sclerotic, or mixed. These lesions usually appear in the medullary cavity, and then spread and destroy the medullary bone and the cortex.

Diagnostic work-up of bone metastases – the role of PET/CT scans, selected radiotracers, and molecular targets

Modern work-up of bone metastases utilizes PET/CT scans, radiotracers, and molecular targets for diagnosis and treatment. A positron-emission tomography (PET) scanner can be combined with a CT scanner into a single machine, which simultaneously provides metabolic information from the PET scanner, and anatomic information from the CT scanner. The PET-CT scans are characterized by higher diagnostic accuracy, better guided biopsy techniques, as well as improved treatment planning and response assessment [18, 19]. Bone, lung, liver and the brain are common sites of distant metastases in many breast or prostate cancer patients. In the past, when signs or symptoms of distant metastases were suspected, chest X-ray, liver ultrasound and bone scintigraphy (bone scan) examinations were often performed, as part of the diagnostic work-up. Presently, the main diagnostic tools for the detection of suspected skeletal metastatic disease, and in assessment of treatment response, include 18 F-fluorodeoxyglucose (FDG) PET and F-18 FDG PET/CT scans [20]. In principle, osteolytic lesions from glucose-avid primary malignancies are more readily detectable by FDG PET/CT scan, in contrast to osteoblastic lesions, which are more readily detectable by bone scan. Overall, PET/CT scans have been shown to be more specific for metastatic disease than bone scans [21, 22].

Fluorine-18-labeled sodium fluoride (¹⁸F-NaF) is a tracer which is rapidly cleared from plasma. Due to high sensitivity and specificity of ¹⁸F-NaF PET/CT scanning, the detection of occult bone metastases is now possible. This illustrates an advantage over the standard bone scintigraphy (often missing many of these lesions) and expands our armamentarium for oncology patient management [23]. Prostate-specific membrane antigen

(PSMA) is a cell surface transmembrane glycoprotein that is overexpressed on prostate tumor cells. For this reason, it provides a rational target for diagnosis, therapy, and monitoring of PSMA expression changes with non-PSMA-based therapy (e.g.: androgen treatment can suppress PSMA expression) [24].

In diagnostic work-up for bone metastases, the following conditions should be considered in the differential diagnosis:

- osteomalacia or osteoporosis,
- chronic osteomyelitis,
- secondary osteoarthritis, including degenerative lesions,
- stress fractures,
- Paget disease,
- tuberous sclerosis,
- eosinophilic granuloma of the skeleton,
- bone lymphoma.

The life span of patients with metastatic bone disease is usually limited. Pain is usually nonspecific, present during activity, at rest and at night. Many patients with advanced cancer develop bone metastases, which are related to skeletal-related events (SREs), which include pathologic bone fractures, spinal cord compression, bladder and bowel disturbances, mobility impairment and several other complications that can lead to loss of independence, depression, anxiety, and intractable chronic pain [25].

Depending on the patient's clinical condition, in some cases biopsies may be considered. Specimens can be obtained from the most accessible bones, in mechanically safe areas (such as metaphysis vs. diaphysis, acetabulum vs. subtrochanteric femur) [26].

In selected patients with metastatic disease of the spine, percutaneous core needle biopsy or open biopsy may be performed, for diagnostic purposes.

The goals of possible surgical intervention for spinal surgery, in some patients with metastatic bone disease, include:

- pain reduction,
- protection of spinal cord function (via decompressing neural elements, and mechanically stabilizing the spine) [26].

Anterior or posterolateral decompression, combined with anteroposterior reconstruction, may be used in cervical spinal surgery or thoracic and lumbar spinal surgery. In addition, vertebroplasty may be considered, as a minimally invasive treatment option for patients with 1- or 2-level vertebral body compression fractures [26]. Also, when a bony site presents radiographic and clinical evidence of a pathologic fracture, surgical stabilization may be indicated (e.g., prophylactic fixation of an impending fracture), since it increases the patient's ability to regain function [26].

Non-pharmacological and pharmacological management of skeletal health – prevention and treatment of bone complications due to advanced cancer

Since bone is the preferred site of metastasis for many solid tumors, multiple complications of bone metastases often result in significant skeletal morbidity, including bone pain, pathologic fractures, spinal cord compression, and hypercalcemia of malignancy. In addition, some cancer treatments have been associated with bone loss (e.g., hormone-modifying therapies in breast and prostate cancer). Therefore, strategies to reduce skeletal-related morbidity should include a proper blend of lifestyle modifications, calcium and vitamin D₃ supplementation, and pharmacotherapy, especially in patients at high risk for SREs or osteoporotic fractures (e.g. patients with prostate cancer receiving androgen deprivation therapy, ADT).

To minimize bone loss in patients with advanced cancer, specific changes in both physical activity level and diet have been recommended. They include a combination of weight-bearing aerobic exercise (such as stair climbing or walking) and muscle strengthening (such as light weight-lifting), adjusted to each patient's condition, that can lead to a desirable increase of the bone and muscle strength and, in consequence, to reduction of the risk of falls, when practiced systematically, with moderate intensity, under supervision [27].

Simultaneously, nutritional interventions (based on comprehensive dietary assessment of each individual patient) are necessary to improve and maintain bone and muscle mass. They include, on average, the dietary intake of 1200 mg/day of calcium and 800 IU/day of vitamin D₃, in addition to sun exposure for 15 to 30 min daily [28, 29]. Numerous studies have revealed that vitamin D₃ supplementation decreased cancer mortality and all-cause mortality. On the other hand, it has been reported that combined vitamin D₃ and calcium supplements increased nephrolithiasis among some cancer patients. To address these controversial issues, more clinical trials on vitamin D supplementation, evaluating exact doses of vitamin D₃, and benefits and risks in different cancer patient populations, are necessary. According to the recent recommendations of the Institute of Medicine (IOM), different measurement values to define vitamin D₃ deficiency should be used, including deficient (meaning insufficient protection against fractures), sufficient, and optimal serum concentrations of 25(OH)D (a vitamin D₃ marker) for different age groups. For instance, for adults below 64 years of age, a daily intake of 400–800 IU of vitamin D₃ (optimal 25(OH)D concentration in the range 50–75 nmol/l), and for adults above 65 years of age, a daily intake of 800 IU (optimal 25(OH)D

concentration in the range 75–100 nmol/l) have been recommended [30].

Among pharmaceutical agents, bisphosphonates provide significant benefits to patients with bone metastases, by decreasing skeletal complications and reducing bone pain. Bisphosphonates are bone-targeted medicines that decrease bone resorption and increase mineralization by inhibiting osteoclast activity, and inducing their apoptosis. Two classes of bisphosphonates are:

- non-nitrogen-containing – such as etidronate, clodronate and tiludronate, and
- nitrogen-containing (more potent osteoclast inhibitors) – such as pamidronate, alendronate, ibandronate, risedronate and zoledronic acid [31].

In addition, denosumab, a monoclonal anti-RANKL antibody, was reported to reduce the risk of SREs among patients with bone metastases caused by prostate cancer, breast cancer, non-small-cell lung cancer, and some other solid tumors [32]. According to the recent guidelines from the American Society of Clinical Oncology (ASCO), there is insufficient evidence to recommend one bone-modifying medication (e.g. zoledronic acid, pamidronate, or denosumab) over another in the management of metastatic bone disease [33].

The recently introduced Alpharadin (radium-223 chloride), which is an α particle-emitting radiopharmaceutical, displayed targeted uptake in areas of osteoblastic lesions. A phase III trial (ALSYMPCA) demonstrated improvements in overall survival of patients with castration-resistant prostate cancer and multifocal symptomatic bone metastases. Adverse events were limited to gastrointestinal and hematologic effects. These promising findings suggest that Alpharadin can be used in the future in the management of different metastatic cancers [34].

Considering associated risk factors for thrombosis among patients with metastatic cancer, prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) is mandatory, as well as adequate pain control with correctly selected analgesics [35].

Radiation therapy

Patients with metastatic bone disease can be treated with radiation therapy. It should be emphasized that the efficacy of radiation therapy is dependent on the radiosensitivity of the tumor [36]. In general, once skeletal metastases are present, patient survival is usually shortened (on average by about 30 months). In spite of that, some patients, even elderly ones, may survive and remain relatively active for various periods of time [37, 38]. Overall, patients with metastatic bone disease should be managed by a team, including specialists in radiation and medical oncology, as well as palliative care experts.

Individualized approach to cancer patients – management of common symptoms, care and support

How primary care physicians, oncology or palliative care specialists and pharmacists might approach these topics individually with patients, and coordinate their care, during usually short follow-up visits remains open and difficult. However, these unavoidable issues have to be considered in a unique patient, family, and medical provider context.

It is important to gently let the patients know some information about their diagnosis, and then, when they are “ready” to confront the situation, to tell them the truth about their serious disease. On the other hand, it is crucial to maintain hope, and let the patients know that the whole team will continue to care for them, until their last moment of life. In particular, patients must be assured that their pain, and many other bothersome symptoms, will be controlled, as much as possible, and their QoL and dignity will be maintained [1, 2].

The importance of maintaining hope, as the disease progresses (e.g. follow-up diagnostic findings are adverse, despite therapy, or treatments are toxic and unsuccessful) should be recognized. For instance, patients and their families should concentrate not on the stereotypical question “how much time do I have?”, but rather, they should focus on the quality of their time “here and now”, and on activities that they still can do (which are important or comforting to them).

Also, in assessing and managing the symptoms of advancing disease and disease burden, it is important to ask specific questions, such as:

- Does the patient have bone or muscle pain?
- Does the patient have poor appetite or constipation?
- Does the patient have shortness of breath or persistent cough?
- Does the patient have problems with sleep?

To inquire about these symptoms is particularly important, since some patients might think that these complaints are just parts of their incurable disease, and cannot be controlled.

During metastatic disease management, it is important to understand what causes the particular symptoms, and which non-pharmacologic and pharmacologic modalities should be considered, and then tried, under medical supervision. If strong medications need to be used, for instance narcotic opioids for intractable pain, then the patients must be briefly educated about several issues, including safety (e.g. driving) and side effects (e.g. constipation, nausea, pruritus, or sedation).

Older patients, who received for example radiation therapy, may complain about different mental symptoms, such as forgetfulness, inappropriate

affect, and changes in their bowel and bladder habits. In addition to therapy, it is necessary to give these patients advice on how to handle these symptoms [1, 2].

Moreover, it is important to help patients with strategies for memory and cognition, so that they can still preserve a relatively good level of functioning. Simple techniques for better remembering include making notes, keeping reminders in the calendar, and creating structured ‘working patterns’ for many routine daily activities (e.g. cooking, shopping). Of course, assistance and supervision by family members is of utmost importance.

In terms of the family support, when the patient is unable to eat, and the family is frustrated about poor appetite and associated weight loss, it is crucial to make sure that the family understands that pressuring the patient to eat may not be helpful, and perhaps may even be counterproductive. At this point, arranging a nutritional consult to focus on palatable, highly caloric, as natural as possible (minimally processed) food that the patient is going to consume in small amounts, on a regular schedule, can be beneficial. Also, when patients are on high doses of narcotic pain medication, constipation is a big concern, and an appropriate ‘bowel program’ needs to be introduced and maintained.

Assessment and management of pain is part of QoL. Pain is called “the sixth vital sign”, and patients are usually open about the degree of pain that they experience. Assessing pain can be done by asking the patient to rate his/her pain level on a scale from 1 to 10, or on a visual analog scale (VAS). Pain may also be an important sign of oncological emergency. In such a situation, an evaluation and plan of action needs to be developed in the context of the entire clinical picture. In addition, precise assessment of the patient mood, using some objective and patient-friendly psychometric tools, can be very helpful. For example, one such instrument – the Polish version of the Hospital Anxiety and Depression Scale (HADS) – has recently revealed satisfactory psychometric properties. However, the Polish version of HADS has been explored only in a selected population of non-oncologic patients. Perhaps in the future, after an extensive HADS validation across various clinical populations in Poland, this world-wide used instrument might eventually be applied as an indicator of the degree of emotional distress often experienced by cancer patients [39].

Impact of pharmaceutical care on adherence to treatment in patients with cancer

The pharmacist’s role in providing pharmaceutical care for oncology patients has been constantly evolving, over the past several years, both in hos-

pital and ambulatory care settings. Currently, pharmacists, especially those specializing in oncology, participate in designing, monitoring, and adjusting chemotherapy protocols. They are actively involved in hospital rounds, on a daily basis, for patients receiving chemotherapy. Their duties also include formulating supportive care plans for chemotherapy induced toxicities, infections, as well as for multiple underlying comorbidities, such as diabetes mellitus type 2, arterial hypertension, coronary artery disease, congestive heart failure, dyslipidemia, and other common chronic diseases.

In addition, in collaboration with physicians, the pharmacists monitor the patient safety, and report adverse events, relevant to every stage of the treatment [20]. Also, pharmacists who have completed additional training in psychology are instrumental in helping cancer patients understand and manage long-term psychophysical adverse effects of their anti-cancer medications. Moreover, pharmacists play a crucial role in helping patients with cancer achieve better medication compliance, via interventions, including face-to-face consultations, written materials, and telephone follow-up calls, which significantly improved the patients' adherence to therapy [40, 41].

Finally, the pharmacists serve as invaluable experts, collaborating with physicians, nurses, and patients in order to detect and manage any potentially harmful drug-drug and drug-diet interactions. It should be emphasized that their involvement in long-term cancer care, in both the inpatient (e.g. hospitals, stationary hospice, and skilled nursing facilities) and outpatient care setting (e.g. home health care, and home-based hospice services), demonstrated the added value of pharmaceutical care to the interdisciplinary, comprehensive care model for patients with cancer, including advanced stages with metastases.

Setting the patients' goals, focusing on their quality of life

In general, it is well known that the quality of life (QoL) depends on many factors, including age, sex, level of education, place of residence, current disease status, and concomitant illnesses. In considering QoL, it should be underlined that everyone is different, and the individual patient's preferences should be respected. Every patient has his/her own definition of QoL, which may be different from the family members' perspective. Therefore, discussing this issue with the patient first is extremely important. Also, addressing QoL with the patient's family members is necessary to make a balanced plan of care. When the disease burden increases, the focus of care needs to change. Patients need to be assured that their QoL is a priority, and that their treatment will be adjusted, as

palliative care services will be involved. In setting the patients' goals, in terms of their QoL, it is necessary to individualize the type of care that will be provided. Thus, emphatic listening to patients' wishes, and respecting their choices, relevant to their approaching disease stages and end of life, are mandatory. Moreover, considering other components, such as family dynamics, social, spiritual and cultural factors, can help in achieving better patient outcomes, especially since many patients with metastatic disease are now living longer, with the advent of many novel therapies.

Integrative approach for patients with advanced cancer, and its beneficial impact on the healthcare costs

An integrative, patient-centered approach illustrates a possibility to use evidence-based complementary and alternative medicine (CAM), along with standard treatment, in order to really improve QoL and fulfill many unmet, complex needs of cancer patients. CAM modalities (such as dietary supplements, vitamins, botanical preparations, massage therapy, breathing exercises, meditation, and many other techniques) that are properly combined with conventional therapies, have been shown to reduce patients' need for medications to manage the symptom burden. Moreover, CAM strategies can decrease recurrence and mortality in some cancers, and improve adherence to conventional treatments, along with sense of hope, empowerment, and emotional well-being, which are invaluable for patients with malignancies [42]. According to a recent study (conducted at Beth Israel Medical Center in New York), an integrative, patient-centered team approach to cancer care that included holistic nursing, moderate physical activity (e.g., yoga therapy program), and a healing environment, in the inpatient setting, saved a substantial amount of money, mostly by reducing the use of adjunct medications, to treat anxiety, insomnia, nausea, and pain. Based on a conservative estimate, total cost savings from decreased medication use were about USD 977 184 annually (calculated as average savings of USD 156 per patient, per hospital day, on the 24-bed unit, working on weekdays only, 261 days per year). Considering that only about 50% of the patients on this hospital unit will use the integrative services, the total healthcare cost savings would be close to USD 488 592 annually [43, 44].

It is important to realize that the ongoing benefits for the cancer patients are sustainable, and also the relevant cost savings usually continue for the duration of the integrative care programs. Of course, CAM therapies for cancer patients should be guided by research, clinical judgment of therapeutic teams, safety procedures, and close col-

laboration between patients, their families and medical personnel. The U.S. National Cancer Institute (NCI) has been committed to CAM scientific research, and to an integrated care approach, to bridge together various healthcare resources, necessary to improve management of cancer patients. Unquestionably, more cost-effectiveness oriented studies, focused on various integrative medicine interventions, or their optimal combinations, coordinated with standard treatment, both in inpatient and outpatient oncology settings, should be conducted in the future.

Conclusions

The term “metastatic cancer” has usually been considered as an indicator that the disease trajectory was coming to an end. However, now we know that this is not entirely true anymore, since our patient populations are very diverse. Furthermore, our treatment options have greatly improved, so that patients are living much longer, even with liver or bone metastases, and their symptoms can be successfully managed, to provide relatively good comfort until the end of life.

In order to accomplish that, primary care physicians, oncology and palliative care specialists involved in the continuum of the patients' management, in collaboration with pharmacists, psychologists, nurses and physical therapists, should be attuned to promptly identify the issues which are important for clinical decision making. This coherent team approach will help patients at every step, and will involve family members and caregivers in regular, active participation in care of their ill relatives. Providing education to the patients with metastatic disease and their families is paramount to pharmaceutical care, and in consequence, it may alleviate suffering, and support the oncology or palliative care therapeutic efforts.

Unfortunately, in reality, many older patients are not even considered for some available therapeutic choices, since their physicians believe that they are “too old” or have multiple comorbidities. This stereotype is unacceptable and should be changed. Moreover, this is incompatible with some recently published research results, relevant to the elderly patients (over 80 years of age), who were qualified to receive modern cardiac revascularization procedures, benefited from them, and enjoyed better QoL, compared to their counterparts who underwent non-invasive treatment modalities [45]. This valuable lesson learned from the field of cardiology should shed some light on the decision making process in many complicated cases, and also could reinforce individualization of care, depending on the specific clinical context of the malignancy.

In addition to the incurable and progressive neoplastic disease, many elderly patients face

some artificial barriers to medical care, which include not only financial costs of treatment, but also unsubstantiated beliefs or biases, and often exaggerated concerns about the patient's status. It should be emphasized that although more research is still needed in this field, elderly patients with painful bone metastases, in addition to necessary comfort care, should be offered (at least for consideration) some reasonable options of palliative radiotherapy, and safe pharmacotherapy, similarly to their younger counterparts. Therefore, good cooperation of medical practitioners, who are involved in every step of the cancer patients' management, across the malignancy spectrum, is crucial to improve outcomes, quality of life, and dignity of these patients. This approach can also reduce unnecessary medical expenses, and alleviate the burden of oncology and palliative care for our society and the entire health care system.

Conflict of interest

The authors declare no conflict of interest.

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