PALLIATIVE CARE NETWORK OF WISCONSIN

Fast Facts Core Curriculum

Cancer Syndromes

PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #62
EARLY DIAGNOSIS OF EPIDURAL METASTASES

David E Weissman MD

Background Epidural metastases are very common in patients with advanced cancer. Cancers most often associated with epidural spread include lung, prostate, breast, kidney, myeloma and melanoma. They are also common in testicular cancer, lymphomas, and Hodgkin's disease. Ovarian and pancreatic cancer rarely lead to epidural metastases. Tumor reaches the epidural space via contiguous spread from adjacent vertebral body metastases or, less commonly, from direct extension of tumor through the intervertebral foramina from adjacent tissue (e.g. retroperitoneal lymphoma or posterior lung cancer).

The importance of early diagnosis Back pain is the herald symptom of epidural metastases; occurring, on average, many weeks to months prior to any neurological damage. That is, pain occurs long before there is any direct compression of the spinal cord, at a time when early diagnosis can be established and treatment started. *Neurological deficits from spinal cord compression are a late finding of epidural metastases; serious damage is usually preventable by early diagnosis.*

Characteristics of pain from epidural metastases Pain from epidural metastases occurs due to vertebral body fracture, structural spine instability, periosteal or nerve root irritation. The various descriptions of pain from epidural metastases are protean. Most commonly, patients say it is 'dull' or 'aching,' often with a sensation of 'muscle spasm.' Pain typically worsens gradually, so that over a period of weeks patients require increasing analgesics and have a corresponding decrease in function. This is in contrast to benign compression fractures, where severe pain occurs suddenly, followed by slow improvement over weeks. If there is nerve root irritation, patients will describe neuropathic symptoms in a radicular pattern (e.g. burning or shock-like pain, and/or dysesthesias). The pain is usually located in the central back or paravertebral region and/or in a radicular distribution. Commonly missed radicular symptoms are tip of shoulder pain from C7-T1 metastases; lateral or anterior rib pain from thoracic metastases; anterior abdominal, flank or hip pain from T12-L2 metastases. Pain is often made worse by increasing the spinal cord load that occurs with standing, coughing or valsalva. Pain in the thoracic region is particularly worrisome due to the narrow spinal canal and minimal epidural space; patients with thoracic metastases often complain of increasing pain when recumbant.

Diagnostic strategies The key to early diagnosis is a high index of suspicion. A good rule to use is that the cancer patient with progressive back or radicular pain, for more than 1-2 weeks, has epidural metastases unless proven otherwise; this is especially true in the high risk cancers (breast, prostate, lung, myeloma). Various protocols describing diagnostic approaches have been developed to aid clinicians (see references); all agree that in the setting of a normal neurological examination, early radiological imaging is essential for diagnosis and treatment planning. Rodichok et al demonstrated in 1981 that plain spine x-rays, in the region of back pain, can be an excellent first screening tool; MRI is the definitive diagnostic study and is necessary for planning radiation or surgical intervention. If neurological signs have become evident, emergent MRI is the diagnostic test of choice.

Summary/Key Teaching Points:

- Epidural metastases (tumor in the epidural space), occurs prior to actual spinal cord compression and neurological damage.
- Pain will precede neurologic deficits by weeks to months.
- Early diagnosis will preserve neurological function.
- Progressive back or radicular pain is an indication for radiographic investigation to rule out epidural metastases, especially in high risk cancers.

References
1. Schmidt MH, Klimo P Jr, Vrionis FD. Metastatic spinal cord compression. *J Natl Comp Cancer Network*. 2005; 3(5):711-9.
2. Byrne TN. Spinal cord compression from epidural metastases. *NEJM*. 1992; 3217:614-619.
3. Rodichok LD, Harper GR, Ruckdeschel JC. Early diagnosis of spinal epidural metastases. *Am J Med*. 1981; 70:1181-1188.
4. Posner JB. Neurologic complications of cancer. *Contemporary Neurology Series, Vol 45*. Philadelphia, PA: FA Davis; 1995.

Version History: This *Fast Fact* was originally edited by David E Weissman MD. 2nd Edition published July 2006; 3rd Edition May 2015. Current version re-copy-edited April 2009; then again May 2015.

Fast Facts and Concepts are edited by Sean Marks MD (Medical College of Wisconsin) and associate editor Drew A Rosielle MD (University of Minnesota Medical School), with the generous support of a volunteer peer-review editorial board, and are made available online by the Palliative Care Network of Wisconsin (PCNOW); the authors of each individual *Fast Fact* are solely responsible for that *Fast Fact's* content. The full set of *Fast Facts* are available at Palliative Care Network of Wisconsin with contact information, and how to reference *Fast Facts.*

PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #135
NEOPLASTIC MENINGITIS

Fareeha Siddiqui MD, Lisa Marr MD, and David E Weissman MD

Background Neoplastic meningitis (NM) – also known as *leptomeningeal metastases*, *meningeal carcinomatosis,* or *leukemic meningitis*, is a common oncologic complication representing spread of tumor cells to the subarachnoid space (SAS). It is a complication which often portends a very short prognosis.

Epidemiology NM is found in 20% of cancer patients at autopsy. Among solid tumors, NM is common in breast cancer, small cell lung cancer, and melanoma while rare in gastrointestinal and gynecologic cancers. 90% of solid tumor patients with NM have widespread metastatic disease. NM is found in 40-50% of patients with hematological malignancies, mostly commonly the acute leukemias and high-grade lymphomas (such as large cell and Burkitt lymphomas).

Signs/Symptoms Tumor reaches the SAS by hematogenous spread via arachnoid vessels or direct invasion along nerve roots. Cancer cells in the subarachnoid space have the potential to: a) settle in dependent portions of the neuraxis (base of brain/cranial nerves or lower spinal canal), b) grow into the surface of the brain and fill the sulci, and c) block normal paths of cerebral spinal fluid (CSF) flow. Thus, the hallmark of diagnosis is neurological signs/symptoms at more than one level of the neuraxis:

- Brain – headaches, nausea/vomiting, seizure, hydrocephalus.
- Cranial Nerves – diplopia, hearing loss, facial numbness, dysphagia, dysphonia.
- Spinal – radicular pain, weakness (usually legs), parenthesis, bladder and bowel dysfunction.

Diagnosis Lumbar puncture typically reveals a CSF profile of high opening pressure, low glucose, high protein, and lymphocytic pleocytosis. Sensitivity for finding malignant cells is 50- 70% for one sample, increasing to 80-90% with three samples. MRI can identify nodular/bulky areas of disease, hydrocephalus, and/or enhancement of the cortex/tentorium if tumor growth along the sulci leads to neovascularization. NM commonly causes abnormal CSF flow; this can be demonstrated by a radionucleotide cisternogram.

Prognosis and Treatment Patients with breast cancer or hematological malignancies that have not been extensively treated with chemotherapy, have a reasonable chance at remission of their CNS disease if their systemic cancer can also be controlled. In contrast, patients with other cancers (e.g. lung, melanoma) typically have a dismal prognosis (1-4 months) with or without treatment. In fact, the median survival of patients who underwent placement of an implanted intraventricular reservoir (Ommaya reservoir) for intrathecal chemotherapy administration was only 72 days in a multicenter retrospective analysis. Unlike spinal cord compression or brain metastases, there is no accepted role for corticosteroids except in lymphoid malignances. Treatment options include chemotherapy and/or radiation.

- Radiation: Either cranio-spinal irradiation (entire spinal column) or focused radiation therapy to sites of bulky or symptomatic areas (e.g. cauda equina for radicular leg pain).
- Chemotherapy: Options include systemic high-dose chemotherapy (Ara-C or Methotrexate) intrathecal chemotherapy (1-2 times per week) administered either by repeated lumbar puncture or via repeated puncture of an Ommaya reservoir. Commonly used intrathecal drugs include methotrexate or Ara-C.

Summary For many patients, NM represents a pre-terminal diagnosis and no anti-neoplastic therapy is warranted. Establishing the diagnosis in such patients may be important to help prognosticate and to anticipate future neurological problems (e.g. seizures, headache, radicular pain). The decision whether or not to begin anti-neoplastic treatment should be made in consultation with a medical, radiation, or neurooncologist.

References

1. Wasserstrom WR, Glass JP, Posner JB. Diagnosis and treatment of leptomeningeal metastases from solid tumors. *Cancer.* 1982; 49:759-772.

2. Grossman SA, Trupm DL, Chen ECP, Thopson G, Cargo EE. Cerebrospinal fluid flow abnormalities in patients with neoplastic meningitis. *Am J Med.* 1982; 73:641-647.
3. Kaplan JG, DeSouza TG, Farkash A, et al. Leptomeningeal metastases: comparison of clinical features and laboratory data of solid tumors, lymphomas and leukemias. *J Neurooncol*. 1990; 9:225-9.
4. Demopoulos A, et al. Leptomeningeal metastases: a review. *Curr Neurol Neurosci Rep*. 2004; 4(3):196-204.
5. Roguski M, Rughani A, et al. Survival following Ommaya reservoir placement for neoplastic meningitis. *Journal of clinical neuroscience.* 2015; article in press.

Version History: This *Fast Fact* was originally edited by David E Weissman MD and published in April 2005. Version re-copy-edited in April 2009; edited again by Sean Marks MD July 2015 with reference #5 added and incorporated into the text.

PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #151
HYPERCALCEMIA OF MALIGNANCY

Fareeha Siddiqui MD and David E Weissman MD

Background Up to 30 percent of patients with cancer develop hypercalcemia. Approximately 50% of these patients will die within 30 days of a hypercalcemia diagnosis, even if the hypercalcemia is corrected, which suggests that hypercalcemia is a sign of hormonally advanced cancer. It is most commonly associated with squamous cell cancers of lung, head and neck, and esophagus, breast cancer, renal cell carcinoma, lymphomas and multiple myeloma.

Pathophysiology

- Local osteolytic hypercalcemia due to direct effect of bone metastases.
- Humoral Hypercalcemia of Malignancy – secretion of parathyroid hormone related protein (PTHrP) by malignant tumors.
- 1,25(OH)2D (vitamin D) secreting lymphomas.
- Ectopic secretion of authentic PTH (very rare).

Symptoms/Signs Symptoms roughly correlate with the degree of hypercalcemia (corrected) and the rapidity of rise: Mild (10.5-11.9 mg/dl); Moderate (12-13.9 mg/dl) Severe(>14 mg/dl).

- Cognitive: sedation, delirium, coma.
- Gastrointestinal: anorexia, nausea, vomiting.
- Renal: dehydration, polyuria, thirst/polydipsia.

Diagnostics

- Total serum calcium, corrected for albumin (*Formula: [(4 - albumin) x 0.8] + Ca^{++}]*).
- Ionized calcium.
- Renal function, phosphate, magnesium and potassium—monitor during treatment.

Anti-Tumor Therapy Treatment of the underlying malignancy with systemic therapy (e.g. chemotherapy) is essential for long-term management. In cases where further anti-neoplastic therapy is not feasible, the decision to treat or not treat hypercalcemia should be made by careful exploration of the patient's goals of care. In advanced untreatable cancer, the decision to not treat hypercalcemia may be very appropriate.

Supportive measures

- *Saline hydration and loop diuretics:* Normal saline 200-500 ml/hr increases GFR, increases filtered load of calcium, and is calciuretic. Loop diuretics (e.g. furosemide) blocks calcium resorption in the loop of Henle. *Note:* only use diuretics once dehydration has been corrected.
- *Discontinue medications* that can increase serum calcium (e.g. lithium, Vitamin D, supplements containing calcitriol, thiazides, calcium antacids); remove calcium from TPN.
- *Increase mobility* if possible.
- *Bisphosphonates* are the drug class of choice for most patients. They work via blocking osteoclastic bone resorption. Pamidronate and zoledronic acid are used in the US with full efficacy noted 2-4 days after administration; responses last 1-3 weeks. May lead to hypocalcemia or azotemia; use with caution in renal dysfunction. *Pamidronate* = 60-90 mg. Repeat only after 7 days have elapsed after 1st dose. Repeat infusions every 2-3 weeks or longer according to the degree and of severity of hypercalcemia. *Zoledronic acid* = 4 mg (maximum). Wait at least 7 days before considering retreatment.
- *Denosumab* is a human monoclonal antibody that is a potent inhibitor osteoclast mediated bone resorption. In repeated studies, it has led to durable responses in over 60% of patients with hypercalcemia refractory to bisphosphonates. Its cost may be prohibitive in hospice settings.
- *Other Agents: Glucocorticoids* are useful in lymphoid malignancies that secrete 1,25(OH)2 Vitamin D. *Calcitonin* may lead to transient and reductions in serum calcium (12-24 hours). It is administered intramuscularly or subcutaneously; initially 4 units/kg every 12 hours; may increase up to 8 units/kg every 12 hours to a maximum of every 6 hours. *Mithramycin* was the standard agent prior to bisphosphonates; now it is used only rarely due to a higher side effect profile.

Gallium nitrate is usually impractical due to the need for a 5 day IV infusion. *Renal Dialysis* can be used in cases of acute/chronic renal failure.

Summary Hypercalcemia is a common oncologic complication that often portends a very short prognosis. The decision to attempt reversal should be made after first exploring the goals of care and assessing the feasibility of future systemic anti-cancer treatments. Vigorous hydration and bisphosphonates are the cornerstones of short-term hypercalcemia therapy.

Reference

1. Stewart AF, et al. Malignancy-Associated Hypercalcemia. In: DeGroot L, et al, eds. *Endocrinology.* 5th Edition. Philadelphia, PA: Saunders; 2005
2. Roodman GD, et al. Mechanisms of bone metastasis. *NEJM*. 2004; 350:1655-64.
3. Ralston SH, et al. Cancer associated hypercalcemia: morbidity and mortality: Clinical experience in 126 treated patients. *Ann Intern Med.* 1990; 112:499-504.
4. Hu MI, Glezerman IG, et al. Denosumab for treatment of hypercalcemia of malignancy. *J Clin Endocrinol Metab* 2014;99:3144-3152.
5. Gucalp R, Insogna K, et al. Denosumab For The Treatment Of Hypercalcemia Of Malignancy Refractory To IV Bisphosphonates In Patients With Hematologic Malignancies. *Blood* 2013;122: 2536-2536.

Version History: This *Fast Fact* was originally edited by David E Weissman MD and published in February 2006. Version re-copy-edited in April 2009; revised again by Sean Marks MD July 2015 with references #4 and #5 added and incorporated into the text.

Background Malignant pleural effusions can cause dyspnea, cough, and reduced exercise tolerance. Over three quarters of malignant pleural effusions are due to lymphomas or cancers of the breast, lung, and ovary. The average survival of patients with refractory cancer and pleural effusions is 4-6 months (1). Survival is considerably worse for patients with poor functional status due to progressive cancer. This *Fast Fact* reviews key facts regarding effusion management.

Symptom Causality and Goals of Care The cause of dyspnea, even in the presence of a known malignant effusion, is not always evident. Common confounding problems include congestive heart failure, chronic obstructive pulmonary disease, pulmonary emboli, pericardial effusions, parenchymal lung metastases, ascites, and radiation lung injury. A 'diagnostic' therapeutic thoracentensis may be indicated to determine if removal of fluid leads to an improvement in the patient's dyspnea. The decision to proceed with thoracentensis should be made after considering the overall goals of care, functional status, prognosis, and presence of co-morbid conditions. Guidelines suggest that no more than 1.5 L of fluid can be safely removed at any one time to prevent reexpansion edema, but some authors suggest that as much as 20ml/kg of fluid can be safely removed (2).

Management Options:

- ***Repeated thoracentesis*** is appropriate for patients with a short prognosis (weeks). The re-accumulation rate is approximately 98% by 30 days (3). Problems associated with this approach include the need for repeated procedures, pneumothorax, infection, and the development of loculation.
- ***Chest tube drainage alone*** involves the use of a large-bore tube to drain the pleural cavity followed by the tube's removal, without sclerosis. This prevents re-accumulation in 11-40% of patients at 30 days follow-up (4).
- ***Systemic chemotherapy or hormonal therapy*** is the best long-term management option for treatment sensitive tumors (see *Fast Facts* #14, 99).
- ***Chemosclerosis*** requires chest tube insertion followed by instillation of a sclerosing agent. It has a success rate of 70-95% with no fluid re-accumulation at 1 month (if the pleural and parietal surfaces are apposed after drainage and pleural fluid drainage is less than 100 ml/day at the time of instillation) (5). Heavy tumor burden, reflected by low pleural pH (<7.2) or glucose concentration (< 3.3 mmol/L), is associated with a lower success rate and shorter survival (6). Talc is inexpensive and has the lowest re-accumulation rates (3-8% after 30 days), compared to doxycycline and bleomycin (1). Talc is rarely associated with ARDS and systemic embolization; more common side effects are pain and fever. Sclerosis requires a large-bore chest tube which often remains in place for 5-7 days – a major consideration in patients with a short prognosis. Thorascopic installation of talc is the most effective technique in highly selected patients, but it is more costly (7,8). Providing adequate pain management is crucial for chest tube insertion and any sclerosis technique.
- ***Small-bore catheters*** can be inserted radiologically in the ambulatory setting and connected to a drainage bag for intermittent drainage by nurses or family members at home. Chemosclerosis can be accomplished through the small catheter. When done in the inpatient setting, sclerosis via a small catheter has a success rate of 62 to 95%; outpatient chemosclerosis may be less efficacious but there has been no head-to-head comparison.
- ***Tunneled pleural catheters*** are similar to small-bore catheters but involve a cuff which is tunneled under the skin to prevent infections. In a 2012 cost analysis, tunneled pleural catheters were found to be the most cost effective management approach when prognosis was 3 months or less (9). A retrospective study showed symptom improvement in 96% of patients at 2 weeks post insertion; spontaneous pleurodesis was noted in 44% of all patients (10).
- ***Pleuroperitoneal shunts*** are occasionally indicated in patients with intractable effusions and trapped lungs. The shunt drains pleural fluid into the abdomen via a subcutaneous reservoir that the patient must pump ~ 400 times/day. Cost, limited efficacy and frequent malfunctioning all limit usefulness of this procedure. In addition, the development of malignant ascites can occur if the patient lives long enough.
- ***Pleurectomy*** is only indicated in patients who are expected to have a prolonged survival. There is significant associated morbidity (20%) and mortality (10%) (11).

References

1. Belani CP, Pajeau TS, Bennett CL. Treating malignant pleural effusions cost consciously. *Chest*. 1998; 113:78S-85S.
2. Putnam JB,Jr. Malignant pleural effusions. *Surg Clin North Am*. 2002; 82:867-883.

3. Anderson CB, Philpott GW, Ferguson TB. The treatment of malignant pleural effusions. *Cancer*. 1974; 33:916-922.
4. Grodzin CJ, Balk RA. Indwelling small pleural catheter needle thoracentesis in the management of large pleural effusions. *Chest*. 1997; 111:981-988.
5. DeCamp MM,Jr, Mentzer SJ, Swanson SJ, Sugarbaker DJ. Malignant effusive disease of the pleura and pericardium. *Chest*. 1997; 112:291S-295S.
6. Heffner JE, Nietert PJ, Barbieri C. Pleural fluid pH as a predictor of pleurodesis failure: Analysis of primary data. *Chest*. 2000; 117:87-95.
7. Shaw P, Agarwal R. Pleurodesis for malignant pleural effusions. Cochrane Database of Systematic Reviews 2004, Issue 1. Art. No.: CD002916. DOI: 10.1002/14651858.CD002916.pub2.
8. Belani C, Einarson TR, Arikian SR, Doyle J. Cost-effectiveness analysis of pleurodesis in the management of malignant pleural effusion. *J Oncology Management.* 1995; Jan/Feb:24-34.
9. Puri V, Pyrdeck TL, et al. Treatment of malignant pleural effusion: a cost-effectiveness analysis. *The Annals of Thoracic Surgery* 2012; 94:374-380.
10. Tremblay A, Michaud G. Single-center experience with 250 tunnelled pleural catheter insertions for malignant pleural effusion. *Chest*. 2006; 129:362-368.
11. Rusch VW. Pleurectomy/decortication and adjuvant therapy for malignant mesothelioma. *Chest*. 1993; 103:382S-384S.

Version History: This *Fast Fact* was originally edited by David E Weissman MD and published in June 2006. Version copy-edited in April 2009; revised again July 2015 with reference #9 added and incorporated into the text.

PCNOW PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #176
EVALUATION OF MALIGNANT ASCITES

Karen LeBlanc and Robert Arnold MD

Background Malignant ascites is the accumulation of abdominal fluid due to the direct effects of cancer. This *Fast Fact* reviews the causes and diagnosis of malignant ascites. *Fast Fact* #177 will review its treatment.

Pathophysiology The pathophysiology of malignant ascites is incompletely understood. Contributing mechanisms include tumor-related obstruction of lymphatic drainage, increased vascular permeability, over-activation of the renin-angiotensin-aldosterone system, neoplastic fluid production, and production of metalloproteinases that degrade the extracellular matrix. Portal venous compression can also occur from metastatic invasion of the liver, leading to peritoneal fluid accumulation.

Natural History The most common cancers associated with ascites are adenocarcinomas of the ovary, breast, colon, stomach and pancreas. Median survival after diagnosis of malignant ascites is in the range of 1-4 months; survival is apt to be longer for ovarian and breast cancers if systemic anti-cancer treatments are available.

Presentation and Diagnostics Symptoms include abdominal distension, nausea, vomiting, early satiety, dyspnea, lower extremity edema, weight gain, and reduced mobility. Physical exam findings may include abdominal distention, bulging flanks, shifting dullness, and a fluid wave. Plain abdominal x-rays are not specific, but may show a hazy or a "ground glass" appearance. Ultrasound or CT scanning can confirm the presence of ascites and also demonstrate if the fluid is loculated in discrete areas of the peritoneal cavity.

There are many potential causes of ascites in the cancer patient: peritoneal carcinomatosis, malignant obstruction of draining lymphatics, portal vein thrombosis, elevated portal venous pressure from cirrhosis, congestive heart failure, constrictive pericarditis, nephrotic syndrome, and peritoneal infections.

Depending on the clinical presentation and expected survival, a diagnostic evaluation is usually indicated as it will impact both prognosis and treatment approach. Key tests include the serum albumin and protein level and a simultaneous diagnostic paracentesis, checking ascitic fluid white blood cell count, albumin, protein, and cytology.

Classification The old classification of exudative versus transudative ascites has been updated through the use of the serum-ascites albumin gradient (SAAG).

SAAG = (the serum albumin concentration) – (ascitic fluid albumin concentration).

A SAAG $\geq$ 1.1 g/dl indicates ascites due to, at least in part, increased portal pressures, with an accuracy of 97%. This is most commonly seen in patients with cirrhosis, hepatic congestion, CHF, or portal vein thrombosis.

A SAAG < 1.1 g/dl indicates no portal hypertension, with an accuracy of 97%; most commonly seen in peritoneal carcinomatosis, an infectious process of the peritoneum, nephrotic syndrome, or malnutrition/ hypoalbuminemia.

Cytological evaluation is approximately 97% sensitive in cases of peritoneal carcinomatosis, but is not helpful in the detection of other types of malignant ascites due to massive hepatic metastasis or malignant obstruction of lymph vessels.

References

1. Thomas J, von Gunten CF. Diagnosis and Management of Ascites. In: Berger AM, Von Roenn J, Schuster J, eds. *Principles and Practice of Palliative Care and Supportive Oncology*. 3rd edition. Philadelphia, PA: Lippincott, Williams & Wilkins; 2006.
2. Adam RA, Adam YG. Malignant ascites: past, present, and future. *J Am Coll Surg.* 2004; 198:999-1011.
3. Spratt JS, Edwards M, Kubota T, et al. Peritoneal carcinomatosis: anatomy, physiology, diagnosis, management. *Current Problems in Cancer.* 1986; 10:553-584.
4. Becker G. Galandi D. Blum HE. Malignant ascites: systematic review and guideline for treatment. *Eu J Cancer.* 2006; 42:589-97.
5. Aslam N, Marino CR. Malignant ascites: new concepts in pathophysiology, diagnosis, and management. *Arch Int Med.* 2001; 161:2733-7.

Version History: Version copy-edited in May 2009; then again July 2015.

Fast Facts and Concepts are edited by Sean Marks MD (Medical College of Wisconsin) and associate editor Drew A Rosielle MD (University of Minnesota Medical School), with the generous support of a volunteer peer-review editorial board, and are made available online by the Palliative Care Network of Wisconsin (PCNOW); the authors of each individual *Fast Fact* are solely responsible for that *Fast Fact's*

content. The full set of *Fast Facts* are available at Palliative Care Network of Wisconsin with contact information, and how to reference *Fast Facts.*

Disclaimer: *Fast Facts and Concepts* provide educational information for health care professionals. This information is not medical advice. *Fast Facts* are not continually updated, and new safety information may emerge after a *Fast Fact* is published. Health care providers should always exercise their own independent clinical judgment and consult other relevant and up-to-date experts and resources. Some *Fast Facts* cite the use of a product in a dosage, for an indication, or in a manner other than that recommended in the product labeling. Accordingly, the official prescribing information should be consulted before any such product is used.

PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #177
PALLIATIVE TREATMENT OF MALIGNANT ASCITES

Karen LeBlanc and Robert Arnold MD

Background The natural history, presenting signs/symptoms, and diagnostic approach to the patient with malignant ascites are discussed in *Fast Fact* #176; readers are encouraged to read this *Fast Fact* to review the important role of determining the Serum Ascites-Albumin Gradient as a diagnostic and treatment aid. This *Fast Fact* will review treatment approaches.

1. **Diuretics:** Malignant ascites (SAAG < 1.1) generally does not respond to diuretic treatment although no randomized trials have been completed. Patients with evidence of portal hypertension (SAAG > 1.1) are more likely to respond to diuretics.

2. **Paracentesis:** Paracentesis can provide immediate relief of symptoms in up to 90% of patients. Drainage of uncomplicated large-volume ascites (4-6 L/session) can be done safely and quickly in the outpatient setting—including the home—or at the hospital bedside; ultrasound guidance is necessary only when there is loculated fluid.

3. **Drainage catheters:** For patients who require frequent paracentesis, external drainage catheters placed through the abdominal wall allow frequent or continuous drainage of ascites fluid without repetitive needle insertions. Patients or caretakers may perform the drainage, reducing visits to medical clinics. Several types of catheters are available:
   a. Pigtail Catheter: A simple, temporary all-purpose catheter; they are prone to complications when used over an extended duration (peritonitis, accidental removal, leakage, occlusion), hence are rarely used now.
   b. Tunneled Catheter: A catheter that prevents infection by promoting scarring around an antibiotic-impregnated Dacron cuff in subcutaneous tissue. Used conventionally for peritoneal dialysis, it is placed with ultrasound or fluoroscopic guidance and has lower risks of infection and leakage than the pigtail catheter. Complications are reduced by daily drainage for the first two weeks of cuff healing. The *PleurX catheter* is FDA approved for malignant ascites and features a one-way rubber valve to prevent leaks between draining sessions. Tunneled catheters are used in patients with life expectancy of at least one month.

4. **Vascular Shunts:**
   a. Peritovenous shunt (PVS) systems are designed to channel peritoneal fluid and proteins in benign ascites back into the circulation via the superior vena cava. PVS has not been shown to have clinically significant risk of disseminating tumor cells in malignant ascites. A PVS is placed by interventional radiology under conscious sedation, and patients typically require 24 hours of monitoring with a central venous line after the procedure. The best response to PVS (only about 50%) is in ovarian and breast cancers. PVS is recommended only in patients with a life expectancy of one to four months, considering that eventual occlusion rate is up to 24%.
   b. Transjugular Intrahepatic Portosystemic Shunt (TIPS) is a shunt between the portal vein and hepatic vein, designed to reduce portal hypertension and improve sodium balance. Most patients with malignant ascites do not have portal hypertension although TIPS might be helpful in the occasional cancer with evidence of increased portal pressures (SAAG > 1.1).

5. **Hyperthermic Intraperitoneal Chemotherapy (HIPEC):** This procedure is performed by surgical oncology specialists and entails warmed chemotherapy being infused into the peritoneal cavity for a short period of time. Most commonly this procedure is done along with tumor debulking or cyto-reductive surgery (CRS). However, considering that recovery from HIPEC with CRS can take 3 to 6 months, CRS-HIPEC is typically reserved for low-grade appendiceal primary cancers seeing that these cancers are associated with a longer survival. For patients with anticipated shorter survivals,

HIPEC without CRS can be done laparoscopically (and is therefore associated with less morbidity) with high rates of ascites control.

References

1. Thomas J, von Gunten CF. Diagnosis and Management of Ascites. In: Berger AM, Von Roenn J, Schuster J. *Principles and Practice of Palliative Care and Supportive Oncology.* 3rd edition. Philadelphia, PA: Lippincott, Williams & Wilkins; 2006.
2. Adam RA, Adam YG. Malignant ascites: past, present, and future. *J Am Coll Surg.* 2004; 198:999-1011.
3. Spratt JS, Edwards M, Kubota T, et al. Peritoneal carcinomatosis: anatomy, physiology, diagnosis, management. *Current Problems in Cancer.* 1986; 10:553-584.
4. Becker G, Galandi D, Blum HE. Malignant ascites: systematic review and guideline for treatment. *Eu J Cancer.* 2006; 42:589-97.
5. Aslam N, Marino CR. Malignant ascites: new concepts in pathophysiology, diagnosis, and management. *Arch Int Med* 2001;161:2733-7.
6. Smith EM, Jayson GC. The current and future management of malignant ascites. *Clinical Oncology.* 2003; 15:59-72.
7. Pockros PJ, Esrason KT, Nguyen C, Duque J, Woods S. Mobilization of malignant ascites with diuretics is dependent on ascitic fluid characteristics. *Gastroenterology.* 1992; 103:1302-1306.
8. Abeloff M, Armitage J, Niederhuber J, Kastan M, McKenna WG, eds. *Clinical Oncology.* 3rd edition. New York, NY: Churchill Livingstone; 2004: 1199-1205.
9. Covey AM. Management of malignant pleural effusions and ascites. *J Support Oncol.*. 2005; 3:169-73.
10. White MA, Agle SC, et al. Denver peritoneovenous shunts for the management of malignant ascites: a review of the literature in the post-LeVeen era. *The American Surgeon* 2011;77: 1070-1075.
11. Randle RW, Swett KR, et al. Efficacy of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy in the management of malignant ascites. Ann of Surg Onc 2014;21: 1474-1479.

Version History: Current version copy-edited in May 2009; then again July 2015 by Sean Marks MD: references #10 and #11 were added and incorporated into the text.

PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #209
MALIGNANT PERICARDIAL EFFUSIONS

Vincent Thai MD

Introduction Malignant pericardial effusions (MPEs) are a rare complication of advanced cancer, but are associated with high morbidity and mortality. This *Fast Fact* discusses the diagnosis and management of MPEs.

Epidemiology and Prognosis Approximately 10% of patients with cancer develop cardiac metastases, with ~75% of these affecting the epicardium (1, 2). Only a third of these, however, will develop clinically significant MPEs (1). Lung and breast cancers are the most common causes. MPEs are associated with a poor prognosis. Studies suggest a *median* survival of 2-3 months after a MPE is diagnosed, with a *mean* survival of 5 months for solid tumors and 20 months for hematologic malignancies (3, 4).

Physiology and Symptoms The pericardial space is normally filled with <50 ml of serous fluid. As this volume increases due to epicardial or pericardial metastases or lymphatic obstruction, both right and left ventricular failure can occur due to inadequate filling. Signs and symptoms include peripheral and pulmonary edema, chest discomfort, cough, shortness of breath, and orthopnea. Severity of symptoms depends on the volume of the MPE as well as the rapidity of its accumulation; severe cases can present with cardiac tamponade and shock. An echocardiogram is indicated whenever a MPE is suspected. Not only does it confirm the presence of an effusion, but its findings can dictate whether or not urgent treatment is indicated (e.g. if signs of tamponade are evident). A diagnostic pericardiocentesis or pericardial biopsy is sometimes needed to confirm the cause of the effusion.

Treatment Options

- *Systemic chemotherapy or radiotherapy* are effective for chemo- or radio-sensitive tumors such as previously untreated breast cancer and many lymphomas. Reaccumulation rates for both modalities are about 1/3 overall, depending on the patient's overall course and response to therapy (5).
- *Pericardiocentesis* results in immediate symptom relief in most patients, however the effusion may re-accumulate, requiring repeat pericardiocentesis (within 1-2 weeks in some series) (6).
- *Pericardial sclerosis* involves instilling a sclerosing agent with the intention of scarring the pericardium to the epicardium, preventing reaccumulation of the MPE (similar to pleural effusions – see *Fast Fact* #157). Multiple agents have been studied including doxyclycline, minocycline, and bleomycin. Success rates (no reaccumulation at 30 days) are about 70-90% (7, 8). Longer term success rates are undefined due to the poor survival of study patients. The major side effect is chest pain (50-70%), cardiac arrhythmias, and fever (8, 9, 10). In head to head comparisons with doxycycline, bleomycin has been shown to have fewer side effects and to lead to shorter hospitalizations (10, 11, 12).
- *Surgical decompression* therapies range from less invasive (balloon pericardiotomy, subxiphoid or thorascopic pericardiostomy) to more extensive (open thoracotomy with pericardial stripping). A pericardial 'window' (which allows ongoing drainage of fluid externally or internally such as into the pleural cavity) is often created. Case series have suggested reaccumulation rates with surgical therapies are low (less than 15% up to 10 months out) (13, 14, 15).

Decision-Making The treatment of MPEs depends on how urgently treatment is needed, the likelihood of the tumor responding to anti-neoplastic treatments, and the anticipated survival of the patient. A multidisciplinary approach to decision-making, involving input from medical and radiation oncology, cardiology, and thoracic surgery is recommended. Simple pericardiocentesis may be appropriate for patients with short prognoses (<1 month), particularly if their MPE is not expected to re-accumulate in their remaining life-span. A symptomatic patient with no signs of tamponade and a chemotherapy-sensitive tumor such as untreated breast cancer may receive a durable response from a pericardiocentesis for symptom relief, followed by chemotherapy. Patients with longer prognoses (>1 month) who are expected to re-accumulate their MPEs will likely benefit most from sclerosis or surgical decompression; there is no clear evidence currently suggesting one strategy is superior to the other.

Symptom directed care without specific intervention for the MPE is an appropriate option for patients with very short prognoses and for those who decline more invasive treatments.

References

1. Klatt EC, Heitz DR. Cardiac metastases. *Cancer.* 1990; 65(6):1456-59.
2. Abraham KP, Reddy V, Gattuso P. Neoplasms metastatic to the heart: review of 3314 consecutive autopsies. *Am.J.Cardiovasc.Pathol*. 1990; 3:195-198.
3. Moores, D.W, Allen K.B, Faber L.P, Dziuban S.W, Gillman D.J, Warren W.H., Ilves R, Lininger L, Subxiphoid pericardial drainage for pericardial tamponade, *J Thoracic Cardiovascular Surg. 1995;* 109:546-552.
4. Dosios T, Theaskos,N, Angouras D, et al. Risk factors affecting the survival of patients with pericardial effusion submitted to subxiphoid pericardiostomy. *Chest.* 2003; 124:242
5. Lamont E, Hoffman PC. Oncologic emergencies. In: Hall JB, et al, eds. *Principles of Critical Care*. 3rd Edition. New York, NY: McGraw Hill; 2005.
6. Laham RJ, Cohen DJ, Kuntz RE et al. Pericardial effusion in patients with cancer: outcome with contemporary management strategies. *HEART.* 1996; 75(1):67-71.
7. Lashevsky I, Ben Yosef R, Rinkevich D, Reisner S, Markiewicz W. Intrapericardial minocycline sclerosis for malignant pericardial effusion. *Chest.* 1996; 109(6):1452-54.
8. Maher EA, Shepherd FA, Todd TJR. Pericardial sclerosis as the primary management of malignant pericardial effusion and cardiac tamponade. *J Thoracic Cardiovascular Surg.* 1996; 112(3):637-643.
9. Ben Yosef,R, Phefer,R, Ge,A, Catane,R. Management of malignant pericardial effusion *Harefuah*, 1988; 115:138-141.
10. Liu G, Crump M, Goss PE, Dancey J, Shepherd FA. Prospective comparison of the sclerosing agents doxycycline and bleomycin for the primary management of malignant pericardial effusion and cardiac tamponade. *J Clin.Oncol*. 1996; 14(12):3141-47.
11. Yano T, Yokoyama H, Inoue T, et al. A simple technique to manage malignant pericardial effusion with a local instillation of bleomycin in non-small cell carcinoma of the lung. *Oncology.* 1994; 51:507-509.
12. van Belle SJ, Volckaert A, Taeymans Y, Spapen H, Block P. Treatment of malignant pericardial tamponade with sclerosis induced by instillation of bleomycin. *Int.J.Cardiol*. 1987; 16(2):155-160.
13. Galli M, Politi A, Pedretti F, Castiglioni B, Zerboni S. Percutaneous balloon pericardiotomy for malignant pericardial tamponade. *Chest.* 1995; 108(6):1499-1501.
14. Palacios IF, Tuzcu EM, Ziskind AA, Younger J, Block PC. Percutaneous balloon pericardial window for patients with malignant pericardial effusion and tamponade. *Cathet.Cardiovasc.Diagn*. 1999; 22(4):244-49.
15. Ziskind AA, Pearce AC, Lemmon CC, et al. Percutaneous balloon pericardiotomy for the treatment of cardiac tamponade and large pericardial effusions: description of technique and report of the first 50 cases. *J.Am.Coll.Cardiol*. 1993; 21(1):1-5.

Author Affiliation: University of Alberta, Edmonton, Alberta.

Version History: Originally published October 2008; copy-edited July 2015.

FAST FACTS AND CONCEPTS #238
MANAGEMENT OF SPINAL CORD COMPRESSION

Rohtesh S Mehta MD, MPH and Robert Arnold MD

Background Metastatic spinal cord compression (SCC) is a medical emergency; early treatment is associated with less functional disability. Treatment options include corticosteroids, radiotherapy and surgery. This *Fast Fact* discusses management of SCC in adults. *Fast Fact #237* discusses its diagnosis.

Corticosteroids Dexamethasone is the most tested steroid in clinical trials. Studies have shown that steroids provide analgesia and reduce vasogenic edema which may lead to better neurological outcomes. Treatment should be started as soon as diagnosis is made; studies in acute spinal cord injury suggest significant neurological improvement when used within 8 hours of injury. Historically, debate existed between using high dose dexamethasone (100 mg loading, then 96 mg daily) versus moderate dose (10 mg loading, then 16 mg daily). A randomized controlled trial comparing the two doses found no differences in efficacy and thus most give the lower dose. (1) Many studies give the steroids divided 4 times a day (total 16 mg daily), tapered over 10-14 days. Most generally start IV and then switch to PO when patients are “clinically stable” and more definitive therapy (radiation or surgery) has been initiated. Steroids should be tapered as soon as possible to prevent long term toxicities (2). Common short term side effects include hyperglycemia, insomnia and gastric distress. Serious acute adverse effects such as gastrointestinal perforation or bleeding, psychosis, risk of infections and death are associated with high doses only (17%) (3).

Radiotherapy (RT) In the absence of bony instability, RT has historically been the treatment of choice, preferably started within 24 hours of diagnosis. Dose schedule for RT ranges from single fraction 8 Gy to 20 fractions of 40 Gy. One or two fractions of 8 Gy may be preferable in patients with short prognoses and, in one study, had a similar outcome to more prolonged treatment (4). RT results in pain relief in 40-80% of patients and sphincter control in 45-90% of cases (3, 4) when instituted in time. About 90% of ambulatory patients retain ambulation with RT alone, but less than 30% of patients who have lost the ability to walk by the time RT is initiated regain ambulation (3).

Surgery Until recently, surgery was reserved for cases with SCC in a previously irradiated area, neurologic deterioration during RT, spinal instability, or bony compression. However a recent meta-analysis (5) and a randomized controlled trial (6) found better functional outcomes with surgery plus post-operative RT as compared to RT alone. This trial used a newer surgical technique (circumferential decompression, reconstruction and immediate stabilization). 84% of the patients in the surgery group were ambulatory and retained ambulation for a longer time (a median of122 days) after treatment compared to 57% in the RT group (median 13 days). 62% of the non-ambulatory patients regained the ability to walk after the surgery compared to 19% in the RT groups. The surgery group also maintained continence for a significantly longer time (median 156 days vs. 17 days). A more recent retrospective matched pair analysis of cancer patients with SCC comparing RT alone to surgery plus RT did not find any significant differences in outcome between the two treatments (7). Prompt, interdisciplinary evaluation by radiation oncologists and spine surgeons is indicated in order to identify the best treatment course.

Other treatments **Spinal Stereotactic Radiosurgery (SRS)** has an investigational role in adult non-surgical patients with radio-resistant tumor or those with previously irradiated areas. Studies suggest more than 80% improvement in overall neurological function (8). **Transarterial embolization** is another novel investigational treatment. It is generally used preoperatively for hypervascular spinal tumors causing compression, is safe and effective, and can make radical tumor resection possible at times (9). In adults, **chemotherapy** has no role in acute management even in chemo-sensitive cancers because of its slow effect. Although **bisphosphonates** reduce the incidence of skeletal complications of cancer, there are no data to suggest a benefit in treating SCC.

Prognosis Median survival after developing SCC is between 3-6 months in adults. Poor prognostic factors for survival include non-ambulatory status, SCC within 15 months of original cancer diagnosis, presence of visceral or other bone metastases, cancer type (survival is worse for lung cancer and better for myeloma/lymphoma), and rapidity of developing motor symptom (worst if <7 days and better if more than 2 weeks after the onset of symptoms).

Conclusion A loading dose of dexamethasone 10 mg IV should be given as soon as possible after diagnosis, followed by maintenance dose of 4 to 6 mg every 6-8 hours, and referral made for primary surgery (if feasible) with adjuvant RT. If surgery is contraindicated, palliative RT alone is indicated.

References

1. Vecht CJ, et al. Initial bolus of conventional versus high-dose dexamethasone in metastatic spinal cord compression. Neurology. 1989; 39(9):1255-7.
2. Weissman DE, Dufer D, Vogel V, Abeloff MD. Corticosteroid toxicity in neuro-oncology patients. J Neurooncol. 1987;5(2):125-8
3. George R, Jeba J, Ramkumar G, Chacko AG, Leng M, Tharyan P. Interventions for the treatment of metastatic extradural spinal cord compression in adults. Cochrane Database of Systematic Reviews 2008, Issue 4. Art. No.: CD006716. DOI: 10.1002/14651858.CD006716.pub2
4. Maranzano E, et al. Short-course versus split course radiotherapy in metastatic spinal cord compression: results of a phase III, randomized, multicenter trial. J Clin Oncol. 2005; 23:3358–65
5. Klimo P, et al. A meta-analysis of surgery versus conventional radiotherapy for the treatment of metastatic spinal epidural disease. Neuro Oncol. 2005; 7(1):64-76.
6. Rades D, et al. Validation and simplification of a score predicting survival in patients irradiated for metastatic spinal cord compression. Cancer. 2010; 116:3670-3.
7. Rades D, Huttenlocher S. Matched pair analysis comparing surgery followed by radiotherapy and radiotherapy alone for metastatic spinal cord compression. J Clin Oncol. 2010; 28(22):3597-3604.
8. Ryu S, Rock J, Jain R, et al. Radiosurgical decompression of metastatic epidural compression. Cancer. 2010; 116(9):2250-7
9. Kato S, et al. Surgical management of aggressive vertebral hemangiomas causing spinal cord compression: long-term clinical follow-up of five cases. J Orthop Sci. 2010; 15(3):350-6.
10. Rades D, et al. Validation and simplification of a score predicting survival in patients irradiated for metastatic spinal cord compression. Cancer. 2010; 116:3670-3.

Author Affiliations: University of Pittsburgh Medical Center, Pittsburgh, PA.

Version History: Originally published December 2010; Copy-re-edited November 2015.
Fast Facts and Concepts are edited by Sean Marks MD (Medical College of Wisconsin) and associate editor Drew A Rosielle MD (University of Minnesota Medical School), with the generous support of a volunteer peer-review editorial board, and are made available online by the Palliative Care Network of Wisconsin (PCNOW); the authors of each individual *Fast Fact* are solely responsible for that *Fast Fact's* content. The full set of *Fast Facts* are available at Palliative Care Network of Wisconsin with contact information, and how to reference *Fast Facts.*