PALLIATIVE CARE NETWORK OF WISCONSIN

Fast Facts Core Curriculum

Oncology

PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #13
DETERMINING PROGNOSIS IN ADVANCED CANCER

David E Weissman MD

Background *How long do I have, Doc?* is among the most common questions asked by cancer patients, especially when informed that there are no further effective anti-neoplastic treatment options. Although prognostication is not an exact science, there are data to help clinicians provide useful information to patients and families – information critical to making realistic end-of-life decisions and referrals for home hospice service (see *Fast Fact* #30).

Performance Status The single most important predictive factor in cancer is *Performance Status* ('functional ability,' 'functional status'): a measure of how much a patient can do for themselves, their activity and energy level. Patients with solid tumors typically lose ~ 70% of their functional ability in the last 3 months of life. The most common scales used to measure functional ability are the Karnofsky Index (100 = normal; 0 = dead) and the ECOG scale (Eastern Cooperative Oncology Group), (0 = normal; 5 = dead). A median survival of 3 months roughly correlates with a Karnofsky score $\leq$40 or ECOG $\geq$ 3. Newer prognostic scales have been developed to help provide prognostic information (See *Fast Facts* #124, 125).

The simplest method to assess functional ability is to ask patients: *How do you spend your time? How much time do you spend in a chair or lying down?* If the response is >50% of the time, and is increasing, you can roughly estimate the prognosis at 3 months or less. Survival time tends to decrease further with increasing numbers of physical symptoms, especially dyspnea, if secondary to the cancer.

Other Factors Several common cancer syndromes have well-documented short median survival times:

- Malignant hypercalcemia: 8 weeks, except newly diagnosed breast cancer or myeloma (see *Fast Fact* #151)
- Malignant pericardial effusion: 8 weeks (see *Fast Fact* #209)
- Carcinomatous meningitis: 8-12 weeks (see *Fast Fact* #135)
- Multiple brain metastases: 1-2 months without radiation; 3-6 months with radiation.
- Malignant ascites (see *Fast Fact* #176), malignant pleural effusion (#209), or malignant bowel obstruction: < 6 months.
- Modified Glasgow Prognostic Score (mGPS): multiple studies have shown that an increased mGPS -- meaning an elevated serum c-reactive protein and a reduced serum albumin – is associated with a reduced cancer specific survival curve irrespective of cancer type.

Other Comments In general, a patient with metastatic solid cancer, acute leukemia or high-grade lymphoma, who will not be receiving systemic chemotherapy (for whatever reason), has a prognosis of *less than 6 months*. Notable exceptions to this are patients with metastatic breast or prostate cancer with good performance status, as these cancers may have an indolent course. In these patients additional features suggesting short prognosis are needed (declining functional status, dyspnea, weight loss).

Discussing Prognosis When discussing prognosis with patients/families, the following four step approach is recommended: *Preparation; Content; Patient's Response; Close*. Remember to:

- Confirm that the patient/family are ready to hear prognostic information.
- Present information using a range: *a few days to weeks; 2-4 months*, etc.
- Allow silence after you provide information; respond to emotion (see *Fast Fact* #29).
- Use prognostic information for eliciting end-of-life goals (see *Fast Fact* #65).

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PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #14
PALLIATIVE CHEMOTHERAPY

David E Weissman MD

Introduction One often hears the term *palliative chemotherapy*, but what exactly does it mean and how can a non-oncologist decide if it has potential value?

Why is chemotherapy used? From the perspective of the patient with locally advanced or metastatic cancer, chemotherapy is used with one of two intents: Hope for cure or hope for life-prolongation. Oncologists use the term *palliative chemotherapy* as a euphemism for chemotherapy that is not expected to be curative. What about chemotherapy used solely for symptom control—is that a realistic goal? Oncologists will occasionally recommend chemotherapy for symptom control, as there are some clinical trial data that in selected cancers chemotherapy may improve quality of life and/or symptom control, without impacting survival. However, as a general rule, physical symptoms related to the cancer highly correlate with tumor burden; chemotherapy that does not effect tumor growth will generally not improve physical symptoms caused by the tumor.

What information do you need from the consulting oncologist to help a patient decide on the value of chemotherapy in advanced cancer?

1. What is the *Response Rate* of the proposed chemotherapy? *Response Rate* = (# of complete responses + # of partial responses)/total # of treated patients; as studied in clinical trials. To qualify as a Response, the reduction in tumor must last for at least one month:

- *Complete Response* = complete eradication of measurable tumor
- *Partial Response* = ≥ 50% reduction in measurable tumor
- *Progressive Disease* = ≥ 25% growth in measurable tumor
- *Stable Disease* = anything between partial response and progressive disease

Note: response rate data that are generally quoted to patients comes from clinical trials involving closely monitored patients with good performance statuses. The response rates for patients outside of clinical trials can be expected to be lower – See *Fast Fact* # 99.

2. What is the *Median Duration of Response* of the proposed chemotherapy regimen? This number is vital for patients to make an informed decision and roughly correlates to months of added life to be expected if the chemotherapy is effective. The MDR, also known as *Time to Progression* (TTP), can be explained to the patient as: *if the chemotherapy is effective at shrinking or stabilizing your cancer (if you are a chemotherapy responder), you can expect it will work for X-X months.*

3. What is the potential treatment burden? Including acute and delayed toxicities, direct and indirect costs (lost work for family members), need for clinic visits or inpatient stays, need for treatment monitoring (e.g. blood tests, x-rays). See *Fast Facts* # 276 and 277 for a discussion of the role of targeted cancer therapies in limiting the potential treatment burden.

4. How long must treatment be continued? Standard practice is to wait for two full cycles of treatment before assessing response. However, if a patient is progressing during the first cycle, they will almost always continue to progress through a second cycle. For responding patients, chemotherapy is generally continued until there is disease progression or intolerable toxicities.

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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.

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PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #65
RADIATION FOR PALLIATION—PART 1

Carolyn Rutter MD, Candice Johnstone MD and David E Weissman MD

Background Radiation therapy (XRT) is used with palliative intent to improve quality of life by improving function and/or diminishing symptoms – most commonly pain, bleeding, or pressure on vital structures. This *Fast Fact* describes the physiology and methods of delivering radiation therapy; *Fast Fact* #66 discusses common indications for and outcomes of palliative XRT.

How it works XRT is the use of ionizing radiation to damage a cell's DNA. This can happen to a DNA molecule itself via a direct effect of the radiation (this is less common), or indirectly via an oxygen compound (OH, HOOH) which reacts with a DNA molecule (this pathway is more common). Damage only occurs in cells within the *radiation field*—the area through which the radiation beam passes. Both malignant and normal cells within the field are affected. Malignant cells are less efficient at repairing DNA damage and are, therefore, more likely to die. The goal is to design a radiation field that includes all of the tumor cells while excluding as much normal tissue as possible.

Types of radiation therapy XRT can be delivered 1) from outside the body as *external beam radiation* (EBRT*)*, 2) from within the body by placement of a radiation source near the cancer (*brachytherapy*), or 3) as a radio-pharmaceutical given by mouth (e.g. iodine-131) or by intravenous injection (e.g. Strontium^{89}).

Fractionation In EBRT patients typically receive one fraction per day, but other schedules are sometimes used (e.g. *hyperfractionation*, or at least 2 doses per day). *Fractionation* takes advantage of the different rates at which malignant and non-malignant cells repair damage caused by XRT; it gives normal tissues an opportunity to recover while continually reducing the tumor cell population.

Dosing Radiation doses are described in units called *Gray* (Gy) or *centiGray* (cGy): 1 Gy = 100 cGy. Note**:** in the older literature, the term *rad* was used: 1 rad = 1 cGy. A *radiation prescription* includes the site being treated, beam orientation and number (e.g. two beams, AP and PA), beam type (photons or electrons) and energy (in Volts), dose per fraction (typical daily doses for palliative EBR range from 150-400 cGy), number of fractions per day, and total dose. A *radiation boost* is an extra dose of radiation, given during the last treatments, to a smaller field within the original field. The total administered dose is based on a balance between giving enough radiation to control the tumor while respecting normal tissue tolerance to minimize the risk of late side effects. Different tissues have different radiation tolerances; liver and kidney can only tolerate a small total radiation dose (< 2400 cGy), whereas bone and peripheral nerves can tolerate much larger total doses (>5000 cGy).

Simulation Prior to the first treatment, patients undergo *simulation*, where the exact location of the field is mapped. Permanent or temporary marks are placed on the skin to help ensure that the treatment field can be reproduced in the same location at every treatment. Various types of immobilization ranging from standard pads, head cups to customizable devices are utilized depending on the clinical situation.

Delivering EBRT If the radiation prescription calls for daily fractions, patients come to the radiation therapy department once a day, five days a week. While most XRT regimens for curative intent often last 5-7 weeks, most palliative XRT regimens can be condensed to a shorter range of one day (e.g. to relieve pain from bone metastases) to three weeks. Treatments are delivered inside a shielded, enclosed room. A radiation therapist operates the radiation machine (typically a linear accelerator) from outside the room while watching the patient on a camera. Each daily treatment takes only a few minutes and is painless.

Toxicity At least once a week patients see the radiation oncologist to evaluate response and assess/treat toxicity. Toxicity depends upon the area being treated and, except for fatigue, is

limited to tissues within that field. Early/acute toxicities occur during or shortly after treatment and resolve within one to two months (e.g. oral mucositis during oral radiation). Late toxicities occur months to years after treatment (e.g. coronary artery disease following chest radiation). Early toxicity is related to inflammation and death of rapidly dividing cells (such as in the skin or gastrointestinal tract), while late effects result from vascular changes and cell death of slowly dividing cells. Radiation oncologists have a host of medications, salves, and mouth rinses to help alleviate acute toxicities (see *Fast Facts* #121, 130, 185).

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PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #91
INTERVENTIONAL OPTIONS FOR MALIGNANT UPPER GI OBSTRUCTION

James Ouellette DO, Lisa Patterson MD, and Paula Termuhlen MD

B**ackground** Patients with unresectable cancers of the upper gastrointestinal tract often suffer severe symptoms due to pain, nausea and vomiting, weight loss, cachexia, and poor food tolerance. This can be related to gastric and duodenal cancers causing intrinsic obstruction of the intestinal lumen or pancreatic and biliary cancers causing extrinsic biliary compression. Management options vary depending on the site of obstruction, the patient's functional status, the patient-defined goals of care, and estimated prognosis. *Fast Fact* #45 discussed medical management options. This *Fact Fact* reviews interventional approaches for upper GI obstructions, especially when further radiation, chemotherapy, medical management, or curative surgical options are longer helpful. Listed below are treatment options for managing different sites of obstruction (listed from least invasive to most invasive). Management decisions for these problems are complex, requiring a multi-disciplinary approach (involving surgery, gastroenterology, medical and radiation oncology, radiology, and palliative care) to achieve the best possible outcome with minimum morbidity.

Esophageal obstruction

1) External beam radiation therapy (successful in 40% of patients).
2) Endoscopic laser therapy (can be repeated every 4-6 weeks).
3) Endoscopic/fluoroscopic stenting (different stent materials are available for different situations).

Gastric or Duodenal obstruction

1) Nasogastric tube decompression (poor long-term solution due to patient discomfort).
2) Venting gastrostomy tube, which allows for drainage of intestinal contents (can be placed endoscopically, laparoscopically, or with open surgery).
3) Janeway gastrostomy (surgically created gastrocutaneous fistula).
4) Endoscopically/fluoroscopically placed stent across the site of obstruction (e.g. pylorus).
5) Laparoscopic gastrojejunostomy.
6) Open gastrojejunostomy.

If unable to restore continuity of the gastrointestinal tract with a surgical procedure to bypass the obstruction, a combination of a gastrostomy tube with a separate jejunostomy tube can be used. This can provide enteral nutrition to the small intestine while venting the stomach. Patients can enjoy the pleasure of eating, even if the food is drained through the G-tube.

Pancreaticobiliary obstructions

1) Stent placement (plastic or metal) across obstruction through an endoscopic procedure (ERCP).
2) Stent/drain placement across obstruction by a radiologic procedure (transhepatic).
3) Laparoscopic cholecystojejunostomy (after gallstone absence is confirmed).
4) Open choledochojejunostomy, cholecystojejunostomy or hepaticojejunostomy.

Adjuvant medications may augment the efficacy of these interventions.

- Proton pump inhibitor to reduce gastric secretions.
- Sucralfate (Carafate) slurry, 1 gram q6 hours, for patients with ulcerated esophageal or gastric lesions.
- Metoclopramide (Reglan) 10 mg tid to qid, as a prokinetic drug.
- Octreotide (Sandostatin) 50-100 micrograms q6-8 h for high volume output conditions.
- Dexamethasone 4-8 mg per day.

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PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACT AND CONCEPT #99
CHEMOTHERAPY: RESPONSE AND SURVIVAL DATA

Narendranath Epperla MD and David E Weissman MD

Background Key data in the decision process regarding chemotherapy include the response rate, median duration of response, and median survival, along with toxicity and quality of life information (see *Fast Fact* #14). The table below synthesizes data for several common cancers. The data were derived by reviewing standard oncology textbooks, along with a Medline search of recent relevant articles.

Comments on the Response and Survival Data

- All data is for patients receiving ***first-line***, commercially available, oral or IV chemotherapy and/or biological therapy (e.g. monoclonal antibodies).
- 'Response Rate' is defined as the percentage of complete and partial responders in a given trial, where 'Partial Response' = ≥ 50% reduction in measurable tumor for one month.
- Response is typically determined after 2 cycles of treatment (usually one cycle every 21-28 days). Note: patients who progress after 1 cycle will generally continue progressing after two.
- The data reflect mid-point ranges derived from the available clinical trials; most of the data represent combination chemotherapy trials. Note: for certain cancers, the benefit of combination vs. single agent therapy is not proven (e.g. pancreas, biliary, liver).
- This information is not representative of all cancer patients. The data represent the 'best case' outcome, from a population of patients who were in good enough health to participate in a clinical trial (e.g. ambulatory, good functional status). Actual responses and response durations for a non-clinical trial population will likely be poorer.
- Second-line chemotherapy, following disease progression from first-line treatment, can be expected to have a lower response rate and shorter duration of response.
- Median survival data includes both responders and non-responders. Note: patients who respond to chemotherapy typically live longer than those who do not.

	Response Rate	Median Duration of Response	Median Survival
Breast	25-55%	8-12 months	24-36 months
Lung (Non-Small Cell) NSCLC, squamous NSCLC, non-squamous	 20-36% 20-35%	 4-6 months 4-6 months	 6-11 months 10-12 months
Esophagus	30-50%	4-6 months	6-9 months
GEJ	40-60%	6-8 months	9-12 months
Gastric HER2 negative HER2 positive	 20-40% ~50%	 4-7 months 6-7 months	 6-11 months 12-14 months
Pancreas	20-32%	4-6 months	8-11 months
Liver (Hepatocellular-HCC) Non Hepatitis C related HCC Hepatitis C related HCC	25-40%	2-5 months	 6-10 months 14 months
Biliary (Cholangiocarcinoma)	20-35%	4-8 months	9-14 months

Colon	30-45%	8-10 months	16-21 months
Melanoma	15-40%	4-14 months	6-15 months

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PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #129

STEROIDS IN THE TREATMENT OF BONE PAIN

Elizabeth Weinstein and Robert Arnold MD

Background Corticosteroids are recommended as an adjuvant analgesic for cancer-related bone pain. The mechanism of action is likely related to decreasing tumor-related edema or inhibition of prostaglandin and leukotriene synthesis. This *Fast Fact* discusses the use of corticosteroids for painful bone metastases; see also *Fast Facts* #66, 67, and116 about palliative radiotherapy. Steroids have been shown to prevent pain flare associated with palliative radiation of bone metastases.

Dosing The ideal corticosteroid, dose, and duration of therapy for bone pain is unknown; current practice is derived from expert opinion and anecdotal case series. Dexamethasone is commonly used due to its lower mineralocorticoid effect and long half-life, which allows once-daily dosing. One randomized controlled trial demonstrated a decrease in pain scores in patients with cancer-related pain using oral methylprednisolone 16 mg PO twice a day. Other starting dosages reported in the literature include dexamethasone 4-8 mg PO daily, methylprednisolone 16-32mg PO 2-3 times per day or prednisone 20-30 mg PO 2-3 times per day.

Duration of Therapy The optimal duration of steroid therapy is unknown. If no benefit is seen within 5-7 days the drug should be discontinued. If beneficial, the drug should be tapered to the lowest effective dose or, if possible, discontinued to avoid long-term adverse effects.

Side Effects Side effects account for discontinuation of steroids in 5% of patients. Acute side effects include thrush (~30%), edema (20%), dyspepsia and peptic ulcer diseases, psychiatric symptoms (insomnia, delirium and anxiety), and glucose intolerance. Delayed side effects from long term use include adrenal suppression, moon facies/fat redistribution, increased susceptibility to infection, osteoporosis, skin fragility and impaired wound healing. A prospective review of 373 inpatients with advanced malignant disease demonstrated that the side effect profile of dexamethasone and prednisone are similar, although at equipotent doses dexamethasone causes slightly more thrush and psychiatric symptoms and less edema, weight gain and dyspepsia. The relationship between peptic ulcer disease and steroids is controversial; in one nested case-control study it appeared correlated with concurrent NSAID use and a cumulative dose greater than 1000 mg of prednisolone or 140 mg of dexamethasone. Case reports and prospective series suggest that psychiatric symptoms are most commonly seen in middle-aged women, are directly related to dosage, and usually resolve with dose reduction.

Summary Steroids are recommended for use in bone pain, but the choice of dose, duration and specific drug is largely empiric. Steroid toxicities are a concern; the duration of treatment should be minimized to reduce the risk of adverse events.

Resources

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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 neuro-oncologist.

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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.

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PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #157
MALIGNANT PLEURAL EFFUSIONS: INTERVENTIONAL MANAGEMENT

Vincent Thai MD and Ron Damant MD

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).

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Gary M Reisfield MD and George R Wilson MD

Background While several studies have found fatigue to be the single most prevalent, severe, and disabling symptom in cancer patients – exceeding even pain – it remains both underrecognized and poorly treated by physicians (1). This *Fast Fact* reviews diagnostic and treatment approaches in the palliative care setting.

Characteristics of Cancer Related Fatigue (CRF) CRF is a persistent sense of tiredness/ diminished energy related to cancer and/or its treatment, which is not relieved by rest, and which causes diminution in functional capacity and quality of life. Additional proposed ICD-10 features include: diminished concentration; diminished motivation; insomnia or hypersomnia; nonrestorative sleep; short-term memory deficits, and marked emotional reactivity to fatigue that are not primarily consequences of depression.

Causes CRF is often multifactorial, with biochemical, physiological, psychological, and behavioral dimensions that remain poorly defined. Assessment is aimed at identifying correctable causes and determining the impact of CRF on both patients and caregivers. Common causes of CRF include:

- Direct effect from cancer and/or treatments
- Sedating medications
- Deconditioning
- Psychiatric co-morbidities (e.g. depression, anxiety)
- Hypoxemia, or severe anemia (Hb ≤8 g/dL) and possibly moderate anemia (Hb ≤11g/dL)
- Systemic infection and/or or significant organ dysfunction (e.g. heart, liver, kidney, lung)
- Electrolyte abnormalities (e.g. $\downarrow Na^{+}$, $\downarrow K^{+}$, $\downarrow Mg^{++}$, $\uparrow Ca^{++}$)
- Nutritional imbalance/impairment
- Sleep disturbance
- Uncontrolled pain (2)

Specific Treatments should be directed toward correcting identifiable causes, e.g. elimination of sedating drugs, correction of anemia or electrolyte imbalance.

Non-Specific Treatments may help in reduce fatigue, optimize function, and promote adaptation.

- **Education:** Educate patient/family about CRF in order to normalize the symptom and promote adaptation/adjustment through setting realistic goals; modifying and prioritizing activities; and planning activities around diurnal variations in energy levels.
- **Exercise:** A meta-analysis suggested that aerobic exercise can improve cancer-related fatigue symptoms (3). Aerobic exercise (low to moderate intensity; progressive) is ideal, but benefits may also be realized with resistance training (4). A reasonable goal is 20-30 minutes of (cumulative) exercise per day, at least 3 days per week.
- **Drug Therapy:** There is little good data for non-specific drug therapy in CRF. The following drugs have been used with variable success:
  - Psychostimulants: While there is a growing literature on the use of psychostimulants for CRF, there is a lack of good controlled trails. *Methylphenidate*: a meta-analysis indicated superiority of methylphenidate over placebo for treatment of CRF (6). Start with 2.5-5 mg and titrate as necessary to 15-30 mg po at 08:00 and noon. *Modafanil*: pilot studies indicated efficacy in the treatment of fatigue associated with depression, multiple sclerosis, ALS, and HIV with potentially fewer side effects than other psychostimulants. However, a more recent meta-analysis showed no benefit over placebo (5). Suggested initial dosing is 50 mg po qam and titrate as necessary to 200-400 mg po qam. See *Fast Facts* #61 and 259.
  - Corticosteroids: These may provide a modest duration of benefit (2-4 weeks) offset by the potential for significant toxicity (6). Reported regimens have included prednisone 7.5-10 mg po qday; dexamethasone 1-4 mg po qday; methylprednisolone 32 mg po qday.
  - Megestrol acetate: Two double-blind, crossover studies showed reduction in CRF with doses of 160 mg by mouth three times a day (7,8).
- **Dietary Supplements:** Ginseng: A randomized trial of 2000 mg of daily oral ginseng vs placebo showed significant improvement in cancer-related fatigue at 8 weeks with no adverse effects (9). L-carinitine has been investigated for CRF in a non-controlled fashion, but the quality of these studies have been suboptimal.

- **Complementary Therapies:** Acupuncture: a systemic review indicated potential benefit in CRF, but also cited a need for more rigorously designed trials before conclusions may be drawn (10).

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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.

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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.

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FAST FACTS AND CONCEPTS #190
PARENTERAL NUTRITION IN ADVANCED CANCER PATIENTS

Mehrnoush Mirhosseini MD and Robin Fainsinger MD

Background Concerns about anorexia and weight loss are commonly expressed by advanced cancer patients and their families. Parenteral nutrition is a controversial and expensive treatment that is sometimes considered to assist with nutrition in advanced cancer patients. PN involves the intravenous delivery of a mixture of lipids, carbohydrates, amino acids, vitamins, and minerals. This *Fast Fact* reviews the role of PN in advanced cancer patients.

The Problem Weight loss in advanced cancer is frequently due to insufficient caloric intake as well as cancer-mediated hypermetabolism and hypercatabolism. These latter problems are caused by catabolic proinflammatory cytokines and eicosanoids and are responsible for much of the accelerated muscle wasting (cachexia) seen in advanced cancer. Patients and families frequently worry about malnutrition and starvation and request help from physicians to ameliorate these.

The Role of PN PN is usually considered outside the standard of care for most patients with advanced cancer. This is based on clinical research findings and other observations:

1. With a few specific exceptions (such as head and neck cancer patients undergoing radiation therapy), caloric supplementation of any kind has not been shown to benefit advanced cancer patients, and – if indicated – can almost always be achieved enterally.
2. There is no physiologic basis to assume that PN would affect the inflammatory and catabolic aspects of cachexia.
3. PN brings potential risks and burdens: laboratory testing, indwelling intravenous lines, infections, metabolic derangements, liver and pancreatic dysfunction.

Patients with progressive weight loss should have careful clinical assessments for potentially reversible causes (such as inadequate caloric intake or depression). Education and emotional and family support are the cornerstones of treatment otherwise. Drug interventions are an active focus of research although their efficacy remains controversial (see *Fast Facts* #93, 100).

PN guidelines There does remain however a small subset of advanced cancer patients for whom PN may be an appropriate therapy to improve quality and/or length of life. The following guidelines have been suggested to identify patients appropriate for PN:

- Enteral nutrition (including tube feeding) is not an option or there is a specific benefit expected from parenteral nutrition (e.g. inoperable malignant bowel obstruction, short bowel syndrome, and malabsorption). These are patients for whom a non-functional GI tract, and not cachexia itself, is the major problem.
- Death is probable from starvation or malnutrition earlier than anticipated from disease progression alone.
- The patient has a life expectancy of at least several months to allow a proper trial of PN (Karnofsky Performance Scale Score >50 or ECOG performance status ≤2).
- The patient has a good self-assessed quality of life; life-prolongation is consistent with their goals of care and the potential risks of PN are acceptable to the patient.
- The patient or caregiver can safely accommodate PN if at home: the home environment is safe and clean; someone is able to set-up and administer the PN; and the patient can be clinically monitored, including laboratory investigation.
- Typically close monitoring of electrolytes, liver and renal function, and triglycerides is required. In addition, careful assessments of the patient's response to treatment and global clinical course are needed to ensure PN remains an appropriate intervention.

Summary

PN can be an important palliative treatment, but for only a small group of cancer patients. Careful patient selection and monitoring is important to ensure that PN is meeting patient-defined goals of care.

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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.

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PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #236
PHARMACOLOGIC TREATMENT OF ACUTE VENOUS THROMBOEMBOLISM IN PATIENTS WITH ADVANCED CANCER 3RD EDITION

René Claxton MD and Robert Arnold MD

Background Venous thromboembolism (VTE) is a common complication of malignancy which carries a poor prognosis (1). This *Fast Fact* discusses the approach to VTE in patients with advanced cancer.

Does anticoagulation for VTE improve outcomes? There is little randomized, placebo controlled data on anticoagulation for the treatment of VTE (2). The only study comparing heparin and warfarin for acute pulmonary embolism (PE) versus no treatment found a decrease in mortality with a number needed to treat (NNT) of four (3). Data from non-placebo controlled trials shows anticoagulation for acute VTE decreases recurrence (4) and clot propagation (5). Based on this evidence and clinical consensus, anticoagulation is recommended to decrease mortality and VTE recurrence in patients with a new VTE.

What is the best treatment for VTE for cancer patients? Current evidence-based guidelines recommend LMWH instead of oral vitamin K antagonists (e.g. warfarin) for at least 6 months in the treatment of acute VTE for advanced cancer patients, even if the patient has a primary CNS malignancy (6). The CLOT trial (7) demonstrated a decreased risk for recurrent VTE in patients maintained on LMWH versus oral anticoagulation with a number needed to treat (NNT) of 13. The major risk of anticoagulation is bleeding. In the CLOT trial major bleeding occurred in ~5% of patients regardless of the type of anticoagulation. A Cochrane review of LMWH versus oral anticoagulants for VTE in patients with cancer showed a statistically significant decrease in recurrent VTE in favor of LMWH (8). There is emerging evidence that novel anticoagulants like dabigatran (a direct thrombin inhibitor) and rivaroxaban (a direct factor Xa inhibitor) may be equally effective at treating acute VTE in cancer but with less overall associated bleeding (though perhaps more GI bleeding) and less need for serum monitoring (9). Although the use of these agents has greatly increased in the last several years, the role of these novel oral anticoagulants vs more established agents such as LMWH is not yet clearly established (6).

Does the evidence supporting the use of anti-coagulation for treatment of VTE apply to cancer patients with short prognoses? Unfortunately, most studies exclude patients with increased creatinine, those in bed greater than 50% of the day, and those with less than a three-month prognosis (see *Fast Fact* #13). Thus, there are no research data to guide clinicians on the efficacy (does it prolong life or reduce symptoms?), safety (what is the bleeding risk?), and tolerability of treating acute VTE in cancer patients with prognoses of weeks to a few months.

What other considerations should be made in the decision to treat acute VTE in cancer patients with short prognoses?

1. Decide whether to anticoagulate or treat symptomatically. This decision is largely empiric and should be based on clinical judgment about prognosis, symptom burden, and patient preference. For instance, for a patient with a prior history of VTE who remains ambulatory and who develops symptomatic VTE (e.g. a painful, swollen leg), providing anti-coagulation may be appropriate to prevent additional symptomatic events. If this same patient was already bedbound with a prognosis of weeks, it is doubtful anti-coagulation would provide substantial benefit. Though current evidence-based guidelines recommend anticoagulation for incidental VTE in advanced cancer (6), there is no strong rationale for this recommendation when a patient has a prognosis of weeks and the patient's primary goal of treatment is comfort.
2. If anticoagulation is chosen, then determine whether to use an oral vitamin K antagonists like warfarin, LMWH, or a novel oral anticoagulant such as dabigatran or rivaroxaban. LWMH and the newer oral anticoagulants do not require routine laboratory testing, have fewer drug-drug interactions, and are less diet dependent for safe administration than

warfarin. In addition, a patient's INR is highly diet dependent and can rise dangerously in patients with diminishing oral intake, which is common for advanced cancer patients. Hence warfarin may require frequent laboratory monitoring of the INR. However, LMWH and new oral anticoagulants are far more expensive than warfarin; furthermore, unlike warfarin, there is no effective antidote for these agents if the anticoagulant effect as needs to be reversed. Warfarin costs approximately $0.11/day compared to $100/day for enoxaparin. However, this comparison does not take into account the cost of laboratory tests to monitor a patient's INR or the administration costs for patients unable to self-administer LMWH. Given its high cost LMWH may not be available for many patients receiving hospice care.

Bottom Line The patient's prognosis and preferences should be considered prior to starting anticoagulation therapy. Clinicians should work with hospice agencies to determine an affordable plan to safely administer and monitor anticoagulation for acute VTE in hospice patients. Clinicians should prepare patients who decide to initiate anticoagulation for discontinuing it once expected survival is short or worsening risks such as uncontrolled INR become apparent.

*Major bleeding includes any bleeding associated with death, located at a critical site (intracranial, intraspinal, intraocular, retroperitoneal or pericardial area), resulting in the need for a transfusion of at least two units of blood or leading to a drop in hemoglobin of at least 2.0 g per deciliter.

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Mansour Gergi MD and Maria Aileen Soriano-Pisaturo MD

Introduction Although no standardized definition exists, transfusion dependence (TD) usually describes patients receiving regular platelet and/or red blood cell (RBC) transfusions more frequently than every 8 weeks due to persistently low counts (1). Myelodysplastic syndrome, myeloproliferative neoplasms, and leukemias are most commonly associated (2). Transfusion thresholds have been subjects of debate, vary by population, and should answer the goals of therapy. Still, many with life-prolonging goals of care become accustomed to basing the need for transfusion on a diagnostic threshold (e.g. hemoglobin < 7), rather than a specific symptom. As TD patients near the end-of-life, they often face emotionally-wrought decisions about the continued role of transfusions.

Potential Benefits of Continuing Transfusions

- Patients may receive significant improvement in fatigue and dyspnea within hours from RBC transfusions when hemoglobin levels are < 7. These benefits likely dissipate after 13 days (3).
- Platelets transfusions can stop or prevent bleeding caused by severe thrombocytopenia within hours but usually have a life span of only 4-8 days (4). Although the usual threshold at which prophylactic platelet transfusions is considered is 10,000 (5), that threshold and the role of prophylactic platelet transfusions in seriously ill TD patients remains controversial and unstudied.
- A retrospective analysis of dying cancer patients suggested that RBC transfusions were associated with a longer survival (15 days) than anemic patients who were not transfused (7 days), and platelet transfusions increased the interval between hospitalizations from 10 to 16 days (6).
- Regular transfusions based on threshold lab values often become a familiar component of the care plan recommended by the cancer team. Transitioning to a care plan in which transfusions are based on how they feel, not lab values, can therefore be unsettling to patients.

Potential Harms of Continuing Transfusions

- Not only is TD a marker of disease severity, organ damage from iron overload can result from multiple transfusions. Thus, there is a 2.2-fold increase in 1-year mortality risk and a 4-year survival of only 47% among TD patients (7-10).

- Although transfusions often can be coordinated for hospice patients with a specific symptom need, logistical complexities do not allow transfusions to be done in a patient's home.

- For patients who desire to continue regular lab draws and blood transfusions, frequent visits to infusion clinics ensue and are associated with a diminished quality-of-life (8,11). Furthermore, hospice involvement is often delayed, thereby increasing the chances of death in a hospital (11,12).

Counseling Patients and Families A hospitalization due to a major medical crisis often prompts a discussion about discontinuing transfusions in the context of a larger discussion about transitioning to comfort-focused care. This can be a challenging time to discuss transfusion discontinuation, as patients can be overwhelmed by their overall medical situation. The following pearls may assist clinicians:

- Once TD is realized and eventual clinical deterioration is anticipated, discuss the expectations of transfusions along with clinical signs which would suggest an appropriate timing to discontinue them. This would pre-empt initiating such discussions during a time of medical crisis.
- Patient and families may worry about inciting imminent death or demise from discontinuing transfusions. For example, they may have been told that discontinuation of platelet transfusions can trigger massive bleeding. Fortunately, most dying patients who stop platelet transfusions do not suffer significant bleeding and most TD patients live > a week after transfusions are discontinued (6). Transparent disclosure of these prognostic implications may alleviate, not exacerbate, concerns.

- Inquire about ethical, legal, cultural, and/or religious concerns which may lead patients to associate transfusion discontinuation with “giving up” or euthanasia. Involve a chaplain or spiritual leader if concerns are identified.
- If a time-limited trial of continued transfusions is pursued, be specific about signs which would signify an appropriate time to discontinue transfusions. Examples of reasonable “end-points” include: a) an anticipated prognosis of weeks or less; b) platelet values which no longer respond to transfusions; c) a terminally-ill, home-bound patient who develops a moribund functional status, as the burden of transport to an infusion clinic will likely supersede any clinical benefit.
- Involve the patient’s oncologist or hematologist. Patients may need to hear from a trusted clinician that it is ok to stop transfusions.

Novel Programs Open access or concurrent care, is offered by select hospice agencies in coordination with some insurers. Through models such as these, patients who are willing to come into clinics for ongoing blood product transfusions may be able to also have access to an interdisciplinary hospice team. Coordination with clinical social workers can help patients and families explore these possibilities.

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