Quality of Life Issues in Lung Cancer
New Symptom Management Strategies

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Diagnosis and treatment of lung cancer can significantly affect a patient's quality of life. Survival rates are dismal, but improvements have been made in dealing with common symptoms and side effects. This article reviews the nature of the problem, pertinent risk factors, and symptoms associated with nausea and vomiting, cachexia, hypercalcemia, and pain. Physicians, nurses, and other health care professionals can play a vital role in the identification and management of these complications, and thereby help to improve quality of life. *(Chest 1993; 103:515-555)*

Lung cancer is the most common cancer killer in women and men, accounting for 25 percent of all cancer deaths.1 Despite aggressive endeavors toward prevention and early detection, patients usually are diagnosed with unresectable disease and concomitant distant metastasis. Given the low probability for cure, survival rates remain dismal, with 5-year survival estimated at only 10 percent.4 Health care professionals caring for individuals with lung cancer thus face significant challenges.

Along the lung cancer continuum from diagnosis to cure or death, patients may experience a variety of symptoms and side effects associated with the different treatment modalities—ie, surgery, radiation, chemotherapy, and/or biologic therapy—or with the natural progression of the disease. The sites of both primary and metastatic tumors correlate directly with the presence and nature of symptoms in lung cancer patients. Four common clinical manifestations—nausea/vomiting, cancer cachexia, hypercalcemia, and pain—will be reviewed as they relate to persons with lung cancer. New management strategies for symptoms will be discussed with a focus on the art of caring as well as the science of medicine.

**NAUSEA AND VOMITING**

The causes of nausea/vomiting in lung cancer patients are multidimensional and include gastrointestinal disturbances secondary to obstruction, radiation enteritis, and liver metastasis. Nausea/vomiting can also be induced by the central nervous system, due to increased intracranial pressure from metastatic disease to the brain, or by drugs, as in the case of chemotherapy and/or narcotic administration. (The introduction of carboplatin into some lung cancer protocols as a substitute for cisplatin, for example, has decreased the incidence of nausea/vomiting.) Alternately, patients may experience nausea/vomiting as a consequence of hypercalcemia or other electrolyte disturbances, such as hypernatremia, hypokalemia, or metabolic alkalosis, which occur secondary to paraneoplastic syndromes. Usually, the primary treatment of the lung cancer will ameliorate these symptoms, thus decreasing the nausea/vomiting. However, chemotherapy with or without concomitant radiotherapy may itself produce nausea/vomiting.

Unfortunately, patients and their families or friends often believe that nausea/vomiting is essential to the therapeutic activity of the chemotherapy and that relief is not possible. In a survey of patients, being sick, feeling sick, and the thought of coming for treatment were among the top four dreaded aspects of receiving chemotherapy.2 The psychological distress of anticipatory nausea and the accompanying physical symptoms has ultimately led to treatment intolerance. Patients may become noncompliant, may "bargain" with the oncologist, hoping for decreased doses and widened dosing intervals, or may suffer from anorexia and lose weight.

Thus it is important to evaluate the patient before treatment for risk factors that may predict the occurrence of nausea/vomiting. These include expectation or anticipation of nausea/vomiting, constipation associated with narcotic use, concomitant use of medications that may themselves cause vomiting, administration of chemotherapeutic agents with severe emetic potential (Table 1),4 or radiation therapy to chest, whole brain, or abdomen. Younger patients are more troubled with nausea and vomiting, as are angry, anxious, and/or highly intelligent patients, who usually have a higher IQ.4 Patients with a history of alcohol intake who average four to five mixed drinks per day report fewer episodes. Gralla and Osoba2 reviewed the literature and found that the frequency of vomiting was essentially the same in all studies, usually occurring in 10 to 25 percent of patients, but can be considerably higher.

Table 1—Relative Emetogenic Potential of Chemotherapeutic Agents*  

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*Adapted from Wickham.4
colleagues' suggest that receptor sites in this population may be less sensitive to emetogenic stimuli. Nonetheless, a history of alcohol abuse does not imply that antiemetics are not appropriate.

The choice, timing, and use of antiemetics depend on the patterns of therapy-related emesis. The incidence of anticipatory nausea/vomiting (ANV) is 40 percent and is predictable from a patient's history. This occurs in young, depressed, educated female patients who are usually of Latin American, Spanish, or Jewish descent. Also, ANV is commonplace in patients receiving aggressive therapy. Morrow has documented an increase in ANV in patients younger than 50 who experienced uncontrolled nausea/vomiting following previous therapy and who subjectively described symptoms as ranging from moderate to intolerable. Anticipatory nausea/vomiting is characterized by vomiting days to hours prior to treatment. It usually results from operant conditioning and is difficult to manage once begun. Therefore, it is imperative that patients be treated aggressively with antiemetics the first time chemotherapy is administered. Statements like "don't worry" or "try to forget about the therapy" do not alleviate the problem and may exacerbate it. The use of oral or intravenous lorazepam or diazepam prior to chemotherapy administration or the patient's clinic visit can significantly decrease anxiety.

Acute nausea and vomiting, which begins 1 to 2 h posttreatment, may last for 12 to 24 h and then usually resolves. Ensuring around-the-clock administration of a phenothiazine such as prochlorperazine orally or rectally for mildly emetogenic chemotherapeutic agents is usually all that is needed. Prochlorperazine is available in 15 or 30-mg spansules and only needs to be given every 8 to 12 h because of its sustained-release mechanism. For more severe nausea and vomiting, the IV use of dexamethasone, 20 mg, and ondansetron (a serotonin 5HT3 antagonist), 0.15 mg/kg at the start of chemotherapy, is effective in approximately 90 percent of patients. Administering IV ondansetron 4 and 8 h following chemotherapy should cover the problem period adequately, since its average half-life is 4 h. In patients older than 75 years, the half-life of ondansetron increases to 5.5 h. Patients with significant hepatic impairment, eg, those with liver metastasis, or increased total serum bilirubin, increased prothrombin time, or ascites, will require a total dose reduction to 8 mg/day. Ondansetron is currently not available in tablet form, although the IV solution has been administered orally with good results. Adequate antiemetic treatment is often achieved with the use of diphenhydramine, 25 mg IV; metoclopramide, 2 mg/kg IV at 0, 2, 4, and 6 h after chemotherapy; lorazepam, 1 mg IV; and dexamethasone, 20 mg IV at the start of chemotherapy, with a cost savings over the dexamethasone/ondansetron regimen.

Delayed and persistent nausea/vomiting is an additional phenomenon that can occur 48 to 72 h posttreatment and remain for almost 1 week. It is rare in patients whose nausea/vomiting was controlled completely in the acute phase. The incidence in patients receiving cisplatin is approximately 60 percent, and it can also occur in those receiving radiation therapy. Ensuring that the patient has enough antiemetics for home use is imperative.

In summary, choosing antiemetics according to mode of action is critical. The use of appropriate doses and routes for multiple antiemetic agents and scheduling their administration according to the duration of action and the patient's pattern of emesis are important considerations in initiating antiemetic therapy. Monitoring the patient for the incidence of extrapyramidal effects of certain antiemetics, such as sedation, diarrhea, and hypotension, is key for ensuring patient safety and tolerance. Additionally, relaxation techniques, music therapy, psychotherapy, hypnosis, and biofeedback are important adjuncts. Encourage the avoidance of favorite foods during chemotherapy and promote "comfort"/ "sick" foods, eg, tea, toast, crackers, and noncarbonated sodas, to assist in the conditioning process. With these safeguards, nausea and vomiting should no longer be a feared side effect.

Cancer cachexia

Weight loss, loss of appetite and desire for food, and taste changes secondary to chemotherapy are also significant concerns in patients with lung cancer. Inquiring about the patient's appetite, interest in food, and recent weight changes is an important part of an assessment. The causes of anorexia may be the cancer itself, the treatment—chemotherapy or radiotherapy—or treatment complications like infection, obstruction, nausea/vomiting, and diarrhea. The exact physiologic mechanism of cachexia is rather confusing and not well known but may involve the production of inflammatory cytokines, hormone-like protein molecules. A cascade of biologic events that can alter protein, lipid, and carbohydrate metabolism may also occur and lead to severe wasting. Protein depletion can cause skeletal muscle atrophy and myopathy, visceral organ atrophy, and hypoalbuminemia, all resulting in significant body image changes.

Weight loss in cancer patients is known to influence prognosis negatively and usually predicts a poor response to therapy. Additionally, patients will have profound muscle weakness and a loss of physical function, and performance status will decrease. Patients with a poor appetite, weight loss, and a change in body image will suffer from fatigue and depression. Moreover, because loss of appetite has such a negative impact societally, quality of life is also affected. Additional factors in cancer patients that affect food intake negatively should be evaluated, including loss of taste and smell, altered taste of meats, aversion to sweet and bitter foods, nausea/vomiting, sore or dry mouth, difficulty in chewing or swallowing, and diarrhea. Loss of taste and smell is sometimes associated with chemotherapeutic agents, eg, doxorubicin, cyclophosphamide, and cisplatin. Patients who lose more than 5 to 10 percent total body weight, those with malabsorption, long-term gastrointestinal dysfunction secondary to surgery, chemotherapy, or radiotherapy, and those whose food intake diminishes markedly need nutritional therapy. Unless contraindicated, the trend is toward high-calorie food supplements and enteral feedings rather than the more expensive total parenteral nutrition.

The use of megestrol acetate has been extensively studied by Tchekmedjian and colleagues. Eighty-nine patients with advanced cancer, unintentional weight loss greater than 5 percent of ideal body weight, and anorexia who were receiving chemotherapy with or without concurrent radiation therapy were randomized to receive placebo or megestrol, 1,600 mg/day. Patients were excluded if they had a past
medical history of heart failure, edema, hypertension, diabetes, deep vein thrombosis, and/or a diagnosis of breast, ovarian, or prostate cancer. Their Karnofsky performance status was >50 percent. Results indicated that those who received megestrol had improved appetite and adequacy of food intake, which positively affected weight gain. Nausea/vomiting, taste loss, and aversion to sweets decreased. The usual starting dose of megestrol is 160 to 320 mg/day in four divided doses. Patients should be monitored for side effects including edema, diffuse rash, menstrual irregularities, and in males, impotence. A trial of megestrol may have a positive effect on appetite and caloric intake, thereby improving quality of life for lung cancer patients.

Hypercalcemia

Hypercalcemia is a common oncologic emergency affecting 10 to 20 percent of all cancer patients. It is usually seen in patients with high tumor burden or end-stage disease. Approximately 13 percent of all lung cancer patients will develop hypercalcemia, with a higher prevalence in those with large cell or squamous cell cancers; it is rare in patients with small-cell lung cancer. Hypercalcemia is defined as serum calcium >11 mg/dl (normal serum calcium is 8.5 to 10.5 mg/dl). Because calcium binds to serum proteins, the serum protein concentration can distort the true calcium level. Thus, total serum calcium must be corrected. A suggested formula is:

Corrected calcium = measured calcium + 0.8 (4-albumin)

Hypercalcemia can arise through a variety of mechanisms. It can occur in patients with bone metastasis as bone resorption exceeds the rate of bone formation. Intestinal calcium absorption decreases in most oncology patients; thus increased bone resorption coupled with the kidney’s inability to handle the heightened calcium load can precipitate hypercalcemia.

Humoral hypercalcemia of malignancy (HCM) develops in patients with solid tumors with or without bone metastasis. Tumor cells release substances systemically that can increase bone breakdown, e.g., parathyroid-related protein. Tumor cell metastasis in bone can also produce substances that stimulate bone destruction, resulting in local osteolytic hypercalcemia. Other factors contributing to hypercalcemia in lung cancer patients are immobilization, dehydration due to nausea/vomiting, anorexia, polyuria, poor nutrition, generalized wasting, and inappropriate use of diuretics. Signs and symptoms of hypercalcemia can be subtle because they mimic symptoms of advanced disease. Nausea, vomiting, anorexia, constipation, lethargy, drowsiness, fatigue, polyuria, polydipsia, and increased excretion of magnesium, sodium, potassium, and calcium is commonplace during chemotherapy administration or in the presence of metastatic disease and should be assessed. Late changes like confusion, coma, hypertension, and bradycardia are more easily correlated with hypercalcemia.

Hypercalcemia of malignancy can be treated successfully in the majority of patients, but several factors must be considered before therapy begins. The most effective therapy for HCM is clearly treating the underlying malignancy. This depends on previous treatment, refractoriness to therapies, and sensitivity of a particular cancer to new therapy. Three approaches can be taken. Aggressive, emergent treatment for moderate to severe HCM can be started in symptomatic patients whose calcium is 15 mg/dl. Asymptomatic patients with calcium levels <12 mg/dl can be observed, as can patients with severe HCM and few options for treatment of disease process.

The goals of therapy are to decrease bone resorption while increasing renal calcium excretion. Some practical considerations include minimizing immobilization, rehydration with concomitant administration of loop diuretics, and discontinuing medications that may exacerbate hypercalcemia, eg, thiazide diuretics, nonsteroidal anti-inflammatory drugs, calcium supplements, and vitamin D.

Choice of therapy depends on urgency of treatment, renal status, bone marrow reserves, whether the patient is hospitalized, and the physician's preference. Calcitonin has a very rapid onset of action, approximately 4 to 6 h, but its duration of effect is only 24 to 48 h. Plicamycin is contraindicated in thrombocytopenic patients. Gallium nitrate's effect may last 2 to 4 weeks, but it is administered in a 5-day, 24-h infusion that usually requires hospitalization. It is also important to monitor patients for renal insufficiency, which is reversible and related to the gallium dose. Etidronate and pamidronate are bisphosphonates that inhibit osteoclast-mediated bone resorption. Both can be administered in the outpatient setting; response rates for pamidronate are 70 percent vs 41 percent for etidronate. Both drugs are contraindicated in patients with renal failure.

Patients and their families or friends should know the symptoms of HCM so that treatment can be started early. Should a patient be unresponsive to therapy, measures facilitating coping with dying are an integral part of treatment.

Pain

Cancer pain is a challenging, complex clinical problem that can be managed effectively 90 percent of the time using a combination of old methods and new techniques. The World Health Organization estimates that 3.5 million people suffer from cancer pain each day, with a higher prevalence (70 percent) of pain occurring in patients with advanced disease. However, as many as 80 percent of persons with cancer pain do not receive adequate relief. Patients with lung cancer may experience pain as a direct consequence of tumor, as in the case of bone metastasis, which is described as somatic or nociceptive pain. This pain is typically well localized, and nonsteroidal anti-inflammatory drugs are very effective in managing it. Conversely, visceral pain is poorly localized and can be referred to distant cutaneous sites. It is described as crampy, deep, aching, and “squeezing,” with accompanying pressure. It usually arises from thoracic or abdominal viscera as in the case of pleuritic chest pain or liver metastasis. Narcotic analgesics have been used successfully. There is no ceiling effect with morphine, hydromorphone, or fentanyl. All are good choices for acute and chronic cancer pain. What works is dose intensity and dose response. What does not work is inflexibility and empiric decisions on the part of the prescriber.

Continuous-release morphine is a long-acting, slow-release narcotic that can be dosed twice a day (q12h). Patients may require immediate-release morphine for exacerbation of pain. Doses should be titrated every 24 h based on the
use of breakthrough short-acting morphine. Sixty-seven percent of patients receiving controlled-release morphine required daily doses of 120 mg/day or more.\textsuperscript{42} Transdermal Fentanyl is a relatively new technology that is available in patches that deliver 25, 50, 75, or 100 μg/h. There are four layers—peel away strip, adhesive, rate-controlling media, and drug reservoir. Once the patch is applied, steady state is achieved within 8 to 15 h, with an expected duration of effect of 72 h. Should the patient require removal of the patch, drug clearance takes 17 h. Dose titration has been difficult with this medication, and caution is necessary in opioid-naïve patients. Increases in body temperature may speed the release of the Fentanyl. Moreover, most patients will still require oral medication for breakthrough pain.

Cost analysis of these and other narcotics has been compiled. Table 2 lists equianalgesic doses of common narcotic analgesics, the quantity for a 1-month supply, and average wholesale price of these medications.\textsuperscript{43} In this ever-changing cost-conscious health care system, it is crucial that health care professionals be aware of the cost of medications prescribed. Additionally, hidden costs accompany high-technology pain management options with IV, epidural, or subcutaneous narcotic infusion. These include pharmacy mixing services, supplies, patient hospitalization and surgeon’s fees for catheter placement, room charge, pump rental, rescue drugs, home nursing visits, and the per diem fees of home care agencies.\textsuperscript{44} Thus, only when side effects or inadequacy of response preclude the oral route should an alternate route be considered.

Neuropathic or deafferentation pain, described as burning, shooting, stabbing, or causing numbness and tingling, is commonly seen in patients with Pancoast’s or superior sulcus tumor syndrome. The characteristic is caused by shoulder pain that radiates down the arm along the ulnar nerve. The pain is steady, severe, and unrelenting.\textsuperscript{7} Patients complain that even a light touch often causes excruciating pain. This type of pain is due to malignant infiltration that destroys nerves and it responds poorly to narcotic analgesics. A trial of antidepressants may prove helpful, but patients must receive the medication for at least 3 weeks to achieve optimal effect. Anticonvulsants like carbamazepine, 100 to 200 mg twice daily initial doses, may also help alleviate pain.

Besides tumor-related pain, lung cancer patients may also have pain associated with surgery, radiation, chemotherapy, infection, and metabolic imbalances like hypercalcemia. Postoperative pain is well managed with patient-controlled analgesia pumps with hydromorphone or morphine. Clinical practice guidelines developed by the Agency for Health Care Policy and Research provide an excellent resource for surgeons and other health care professionals dealing with acute pain.\textsuperscript{45} At times, clients receiving cisplatin and the vinca alkaloids, vinblastine and vincristine, may develop neuropathic-like pain.

The armamentarium is available to manage cancer pain successfully. The problems lie in its misuse or lack of use. Despite great strides, patients are still at the mercy of a “triple whammy” effect—the physician underprescribes, the nurse undermedicates, and the patient undertakes.\textsuperscript{46} Persons with cancer are fearful of addiction, drug tolerance, and narcotic-induced constipation. All these concerns can be alleviated through education, counseling, and prophylaxis. An Eastern Cooperative Oncology Group questionnaire to member oncologists examined physician practices and attitudes concerning cancer patients’ pain.\textsuperscript{47} Eighty-five percent of respondents reported that cancer pain is inadequately controlled due to poor assessment. Fifty percent believe that patients are reluctant to report pain and take prescribed medications and that their physicians are unwilling to prescribe adequately and/or are not knowledgeable regarding pain management. Nearly 30 percent of these physicians were reluctant to provide aggressive pain control until the patient was considered terminal (life expectancy less than 6 months) due to fears of patient addiction, side effects, and the possibility of drug tolerance.

Barriers to effective pain management can be overcome with enhanced communication, collaboration among health care professionals, and the inclusion of patients and their families or friends in the plan of care.

**CONCLUSIONS**

Quality of life for persons with lung cancer can be maximized with a host of innovative treatment strategies and comfort measures. Individuals with cancer hope for a cure; when that is not realistic, they hope for quality of life for however long it may be. As health care professionals, we have the responsibility to exhaust all avenues to provide this quality of life.

**REFERENCES**

and chronic vomiting: the state of the art. Oncol Nurs Forum 1989; 16:563-74


17. Mundy GR, Martin TJ. The hypercalcemia of malignancy: pathogenesis and management. Metabolism 1982; 31:1247-77


