Cachexia in Patients With Advanced Cancer

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Case Study

B.C. is a 72-year-old female with stage IV metastatic papillary adenocarcinoma of the ovary status post nine cycles of carboplatin and paclitaxel, three cycles of topotecan, and three cycles of weekly paclitaxel. She currently is receiving gemcitabine and arrives today on a stretcher via ambulance saying that her abdomen is getting larger and that she is unable to get out of bed, take care of herself, or eat.

On physical examination, B.C. has pale skin, sclera, and mucous membranes. Her skin turgor is poor. Her gums are red and swollen, and her tongue is coated with a yellow crust. Her hair and nails are brittle. She is not in respiratory distress and rates her pain a “1” on a 0–10 point scale. Her weight is 82 pounds, down 16 pounds since her last visit one month ago (height is 60 inches). Chest auscultation reveals decreased breath sounds bilaterally. Heart sounds are normal with no murmurs, gallops, rubs, or tachycardia. The abdomen has a well-healed midline incision at the time of her last surgery (REE) greater than resting energy expenditure. B.C.’s laboratory study results are listed in Table 1. She is admitted to the oncology unit with the diagnoses of progressive anorexia and altered metabolism.

Cancer cachexia is a term derived from the Greek words *kakos* and *hexit*, meaning bad or poor condition or state of being (Fearon, Barber, & Moses, 2001; Ottery, 1995). This is a syndrome of profound, progressive weight loss and muscle wasting accompanied by anorexia and altered metabolism (Glynn-Tucker, 1998; Smith & Souba, 2001). Cachexia has been described objectively as a decrease in baseline weight by 10% or more in six months or a decrease of 5% of weight in one month (Rozenzweig, 2000). Other clinical manifestations may include early satiety, weakness, fatigue, impaired immune function, decreased motor and mental skills, and decline in attention span and concentration abilities (Ottery). Cachexia is present in almost 50% of patients with cancer at the time of diagnosis and has been shown to be an independent predictor of survival (Dewys et al., 1980; Glynn-Tucker; Ottery; Smith & Souba). According to Ottery, people with cancer who lose 10% of their normal weight do not live as long as those with similar cancers at similar stages who have remained well nourished. Weight loss is seen most commonly in patients with gastric and pancreatic cancer and least commonly in patients with breast cancer and lymphoma (Dewys et al.). The frequency of weight loss increases as the number of metastatic sites increases (Dewys et al.).

Weight loss has a profound effect not only on median survival but also on quality of life. It affects one’s ability to carry on the activities of daily living (performance status), as well as self-image and control (Dewys et al., 1980; Maltoni et al., 2001). Multifactorial causes (i.e., physiologic, psychological, and social) contribute to difficulty in finding treatment. People generally lose weight because of a reduction in food intake, an increase in energy expenditure, or a combination of both. Patients with cancer have specific physical problems, such as obstructions of lumens by tumors or side effects of analgesics or chemotherapy, as well as changes in metabolism, such as glucose intolerance and the secretion of cytokines, that exaggerate these processes (Fearon et al., 2001; Smith & Souba, 2001; Tchekmedyian, 1995). In addition, anxiety, depression, and decreased socialization and performance status further compound the problem. Attempts to reverse severe nutritional depletion usually are unsuccessful (Ottery, 1995). Therefore, early assessment and intervention are necessary to prevent the morbidity and mortality, as well as the higher healthcare costs, associated with cancer cachexia.

1. Which of the following hypotheses traditionally has been used to explain the pathophysiology of cancer cachexia?
   A. Metabolic abnormalities
   B. Direct tumor effects
   C. Treatment side effects
   D. “Host feeding the tumor” effects

2. In assessing B.C., what clinical manifestations of cachexia would the nurse be looking for?
   A. Decreased motor and physical skills, impaired immune function
   B. Hypothermia, hypertension
   C. Anxiety, distention of jugular veins
   D. Hyperactivity, dietary energy intake greater than resting energy expenditure (REE)

3. Following the patient’s diagnosis of cachexia, the nurse prepares to teach the patient about which of the following therapeutic options?
   A. Caloric supplementation
   B. Use of orexigenic agents
   C. Pharmacologic agents that halt the wasting process
   D. Palliative resection of the tumor

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Question 1: The correct response is choice D. Although many of the physiologic changes of cancer cachexia are similar to those of simple starvation, many others are different because of various factors, such as metabolic effects of the tumor, side effects of treatment, and the mechanical effects of the tumor itself. For example, in starvation, REE decreases with decreased food intake so that the body can conserve vital resources. Fat is used for energy before lean tissues. In patients with cancer cachexia, decreased food intake does not always result in decreased REE. Some patients demonstrate hypermetabolism, and others have no change or a decrease in REE (Fearon et al., 2001; Foltz, 2000; Whitman). Previously, cancer cachexia was believed to result from a tumor “stealing” the nutrient intake of the host and thus causing the host to starve; however, this has not been validated by recent research (Brown, 2001).

Aggressive feeding of patients with cancer cachexia rarely restores the lean body mass of muscles or organs that has been lost (Espat, Moldawer, & Copeland, 1995; Whitman). Patients with cancer who are fed aggressively appear to gain primarily water and fat (Smith & Souba, 2001). According to Smith and Souba, “the actual energy and nitrogen demands of human tumors cannot account for the profound weight loss generally observed” (p. 3013). The total mass of a patient’s tumors rarely exceeds 1%–2% of total body weight, yet patients with even less of a tumor burden may be extremely cachectic (Glynn-Tucker, 1998; Smith & Souba, 2001). Several proinflammatory cytokines, including tumor necrosis factor (TNF or cachexin), interleukin-1, interleukin-6, interferon gamma, and ciliary neurotrophic factor, have been implicated in causing patients with cachexia to decrease their energy intake (by causing anorexia) and to increase their energy expenditure (by increasing their metabolic rate). They do this by causing a variety of changes in the metabolism of nutrients, including altered glucose, fat, and protein metabolism (Fearon et al., 2001).

Table 1. Pertinent Laboratory Results

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient Value</th>
<th>Normal Values</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>1.9 g/dL</td>
<td>3.8–4.5 g/dL</td>
<td>Low levels indicate protein depletion. The test is insensitive to minimal protein deficit. Half-life is 18–21 days, so it does not detect rapid changes in nutritional status. A lower value suggests a poorer prognosis.</td>
</tr>
<tr>
<td>Folate</td>
<td>3.5 mg/L</td>
<td>3.5–25 mg/L</td>
<td>This vitamin is needed for normal red blood cell and white blood cell function, normal DNA replication, and cell division. It decreases in malnutrition.</td>
</tr>
<tr>
<td>Glucose</td>
<td>142 mg/dL</td>
<td>70–105 mg/dL</td>
<td>Patients with cancer cachexia usually exhibit a relative glucose intolerance and increased rates of glucose production and recycling.</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>23%</td>
<td>37%–47%</td>
<td>This is the percentage of red blood cells in a volume of whole blood. It is performed with hemoglobin, and levels parallel each other.</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>7.5 g/dL</td>
<td>12–16 g/dL</td>
<td>This is the main intracellular protein of erythrocytes. Levels decrease with nutritional deficits.</td>
</tr>
<tr>
<td>Prealbumin</td>
<td>3.5 mg/dL</td>
<td>17–40 mg/dL</td>
<td>Indicates whether protein depletion or repletion is present. Half-life is two to three days, so it is useful for monitoring acute changes in protein status.</td>
</tr>
<tr>
<td>Total iron-binding capacity</td>
<td>160 ug/dL</td>
<td>200–310 ug/dL (adjusted for age)</td>
<td>Iron is necessary for erythropoiesis. Unbound iron is toxic, so it travels bound to transferrin. If transferrin is decreased, the ability to bind and transport iron decreases. Total iron-binding capacity is decreased in widespread malignancies and in malnutrition.</td>
</tr>
<tr>
<td>Total lymphocyte count</td>
<td>630 mm³</td>
<td>≥ 2,000 mm³</td>
<td>This is a nonspecific measure of immune function and an indirect measure of nutritional status. Levels less than 1,200 mm³ suggest nutritional deficiency and increased risk of morbidity and mortality.</td>
</tr>
<tr>
<td>Transferrin</td>
<td>85 mg/dL</td>
<td>250–450 mg/dL</td>
<td>Represents visceral protein stores to a greater extent than total protein or albumin. Half-life is 8–10 days. It may be a useful indicator of protein repletion.</td>
</tr>
</tbody>
</table>

Note. Based on information from Espat et al., 1995; Fearon et al., 2001; Jaffe & McVan, 1997.
With cachexia, glucose is overproduced because of increased gluconeogenesis. Glucose intolerance develops with marked resistance to insulin. Anaerobic glycolysis replaces oxidative phosphorylation. Utilization of this anaerobic metabolism pathway takes energy away from the host. As a result, patients may appear to be in a type 2, diabetic-like state (Smith & Souba, 2001).

Elevated fat oxidation rates cause adipose tissue to be lost. This rate elevation decreases the rate of lipogenesis without increasing the rate of lipolysis (Fearon et al., 2001). Body fatty tissue is depleted, and hyperperidemia develops; triglycerides become elevated (Foltz, 2000).

Cytokines cause an increase in the rate of body protein catabolism in patients with cancer cachexia. Patients develop atrophy of the skin and skeletal muscle mass and appear emaciated. Concurrently, circulating levels of the essential amino acid glutamine decrease, which becomes progressively severe with progressive tumor growth (Smith & Souba, 2001). Loss of protein also results in decreased lymphoid tissue mass and a decrease in circulating lymphocytes. Patients consequently become immunosuppressed.

A circulating catabolic factor, 24 K protein, has been isolated from the urine of mice with adenocarcinoma and patients with cancer cachexia. This protein has not been found in the urine of patients with diseases other than cancer, patients with weight loss resulting from trauma, or patients with cancer with little or no weight loss. In the studies of the mice, those pretreated with an investigational monoclonal antibody did not go on to develop cachexia as the untreated mice did (Carluk et al., 1997; Todorov et al., 1996). In the future, a monoclonal antibody for clinical use in treating cachexia may be developed.

Choice B, direct tumor effects, is incorrect, as the tumor itself also is a cause of cancer cachexia. The presence of tumors can cause obstruction and interference with function at any point in the gastrointestinal (GI) tract. For example, tumors in the GI tract may cause mechanical interference with chewing, dysphagia, early satiety, nausea and vomiting, diarrhea, constipation, pain, or the sensation of food being stuck in one’s throat after swallowing. All of these alterations may contribute to patients not wanting or not being able to eat or absorb nutrients.

Choice C, treatment side effects, is incorrect. Cancer therapies affect the ability to chew, swallow, and absorb food. Nausea, vomiting, constipation, physical debility, psychological distress including depression, as well as pain and the side effects of its treatment (particularly with opioids), may cause anorexia. Side effects of radiation (e.g., dysphagia, stomatitis, xerostomia) and chemotherapy (e.g., taste changes, diarrhea, infection, mucositis) also may contribute to anorexia (Fearon et al., 2001). Surgery itself often is associated with a period of malnutrition. Radical resections of the head, neck, or GI tract further increase the potential for malnutrition. Although cancer treatments are aimed at reducing the tumor burden and its effects, they create further malnourishment and cachexia.

Question 2: The correct answer is Choice A. The clinical assessment is a very important component of the nutritional assessment for patients with cancer as nutritional deficits can exist without extreme signs and symptoms (Foltz, 2000). For example, weight loss is overlooked easily in obese or edematous patients if a careful assessment for signs and symptoms of nutritional deficiencies is not performed. Patients with cancer cachexia exhibit decreased motor and physical skills because of muscle wasting and impaired immune function with slower healing as a result of altered protein metabolism. This is in addition to the hallmarks of anorexia, fatigue, and weight loss. Patients also may have dry skin with poor turgor, gum disease, dry or pale oral mucosal, brittle hair and nails, amenorrhea and cold intolerance, and early satiety. Diagnostic tests will reveal decreased albumin, prealbumin, transferrin, folate, and lymphocytes, and increased serum glucose levels. Hemoglobin and hematocrit usually will be reduced unless dehydration is present (Glynn-Tucker, 1998; Rozenweig, 2000).

Choice B is incorrect. No anticipated deviation from normal temperature is expected when cachexia is present. Systolic and diastolic blood pressure values usually are decreased. Tachycardia may be present; respirations will be normal or increased (Glynn-Tucker, 1998). Initially, compensatory mechanisms may be triggered by low blood volume, decreased hemoglobin, and decreased albumin or hypoxia, and result in an increase in heart rate, systemic vascular resistance, preload, and cardiac contractility.

Choice C is incorrect. Patients may exhibit anxiety or symptoms of depression, but jugular vein distention usually is not found as patients tend to have a fluid volume deficit. Low albumin levels further contribute to low central venous pressure as the lack of osmotic pressure causes fluid to leak out of the vascular compartment into the interstitial spaces, producing peripheral edema. Choice D is incorrect. Patients with cachexia are not hyperactive; they are weak and fatigued and have difficulty with activities of daily living. Intake of energy by dietary means usually is low. Although REE varies, elevated REE frequently is found (Bosaeus, Daneryd, Svanberg, & Lundholm, 2001). Bosaeus et al. found that . . . an expected up-regulation of dietary intake in response to elevated energy expenditure is frequently lost in cancer patients. Thus, cancer cachexia may be explained by uncoupling of food intake to energy expenditure rather than by primary alterations in appetite itself (p. 383).

Question 3: The correct response is B, the use of orexigenic agents. If cancer anorexia is a noxious and upsetting symptom for patients and their families, then drugs that increase appetite can be used to help palliate this symptom even though clinical trials have shown that survival is not improved (Jatoi & Loprinzi, 2001). Corticosteroids also may be prescribed for anorexia associated with cancer. Dexamethasone has been shown to affect the appetite as much as megestrol acetate (Loprinzi et al., 1999). However, its side-effect profile includes myopathy, electrolyte disturbances, and fluid retention. Therefore, dexamethasone is indicated only for short-term use. Dronabinol has been shown to increase appetite and mood without affecting weight gain. Side effects include confusion, dizziness, euphoria, and somnolence (Beal, Olson, & Laubenstein, 1995). However, in a recent study of 469 patients with advanced cancer randomized to receive dronabinol (2.5 mg twice daily), megestrol (800 mg per day), or both, megestrol provided superior anorexia palliation than dronabinol, and combination therapy did not confer additional benefits (Jatoi et al., 2002). Cyproheptadine is a histamine and serotonin antagonist that appears to improve appetite in patients with carcinoid tumors (Jatoi & Loprinzi; Kardinal et al., 1990). Pentoxifylline (generally used to treat peripheral vascular disease) appears to inhibit production of TNF and has been studied for use as an orexigenic agent; however, it did not improve appetite in the patients studied (Goldberg et al., 1995). Hydrazine sulfate inhibits the enzyme that drives gluconeogenesis from lactate (Fearon et al., 2001). Hydrazine sulfate has shown
only marginal benefit, if any, in improving weight loss, and one trial showed a trend toward worsening survival and quality-of-life rates (Loprinzi et al., 1994). Therefore, orexigenic agents can be prescribed to patients who wish to increase their appetite.

Choice A, caloric supplementation, is incorrect. Although it appears that an increase in caloric intake would benefit patients with advanced cancer, studies do not support this assumption (Jatoi & Loprinzi, 2001). Studies also have suggested that only three specific instances exist, all occurring in the setting of possible cure, where increased caloric intake may be beneficial. These scenarios include preoperative patients with cancer, patients undergoing a stem cell or bone marrow transplant, and patients being treated for head and neck cancer (Jatoi & Loprinzi). Nevertheless, food has cultural, religious, and psychosocial significance. Therefore, discussing nutritional goals with caregivers and determining whether patients’ quality of life will be improved by caloric supplementation is critical. Caregivers may try to force food on patients, believing that they will live longer if only they would eat. Forcing food can cause discomfort because of early patient satiety, bloating, or dyspnea. Jatoi et al. (2000) found one caregiver who explained why eating was so important at the end of life.

Food, from time immemorial, is part of the nurturing process, and “bread the stuff of life,” all that stuff . . . so when you think of food, you think, well, if you can eat, you can get healthy (p. 2932).

Some patients may experience annoyance or anger when food is pushed on them and they are not hungry. Others are concerned about good nutrition and get upset when their concern is not taken seriously. Whitman (2000) noted that the “eat whatever you want” message can be dangerous as patients may hear “because you are going to die anyway” (p. 123).

Choice C, agents to halt the wasting process, is incorrect as these agents currently are being tested. However, they do show some promising results in modulating the underlying metabolic problems associated with cancer cachexia. The goal would be to allow traditional nutritional support to be more effective when used in conjunction with these agents.

Boasberg et al. (2000) found that thalidomide curtailed weight loss (and improved sleep) in a small sample of patients with advanced cancer, possibly as an effect of cytokine inhibition (Jatoi & Loprinzi, 2001). Nonsteroidal anti-inflammatory agents are being studied because of their ability to reduce levels of some of the proinflammatory cytokines. Preliminary results have shown a modest increase in weight when used with megestrol acetate (McMillan, O’Gorman, & McArddle, 1999). Fish oil (combined with oral nutritional supplementation) has reversed weight loss, improved appetite, increased lean body mass, and improved performance status in weight-losing patients with cancer (Barber, Ross, Voss, Tisdale, & Fearon, 1999). Another study of fish oil with vitamin E suggested that fish oil can prolong survival of malnourished patients with generalized malignancies (Gogos et al., 1998). Fish oil increased the ratio of T-helper to T-suppressor cells and decreased production of TNF (Gogos et al.).

Adenosine triphosphate (ATP), a direct energy source, is being explored for use in patients with advanced cancer with cachexia. Agteresch, Dagnelie, van der Gaast, Stijnen, and Wilson (2000) found that when ATP was given to patients with advanced non-small cell lung cancer, beneficial effects on weight, muscle strength, and quality of life were found. These agents, which require further clinical trials, hopefully will give rise to improved treatments for cancer cachexia in the future.

Choice D, palliative resection of the tumor, is incorrect. Curing the cancer best treats cancer cachexia. Unfortunately, curing cancer is very difficult to do in adults with advanced solid tumors (Fearon et al., 2001). Palliative treatment may decrease contributors to the situation, such as obstruction or pain, but it will not halt adverse metabolic effects of tumors.

Summary

Cancer cachexia generally is considered to be the end stage in the progression of nutritional deterioration and wasting of malignancy (Ottery, 1995). In patients with advanced cancer, this condition is very common and decreases quality of life, as well as survival (Fearon et al., 2001; Ottery; Smith & Souba, 2001; Whitman, 2000). However, if early diagnosis and intervention can control cachexia, the potential exists to greatly improve a patient’s quality of life and prolong survival. Because metabolic alterations inhibit the effective use of conventional nutritional support, anti-inflammatory agents or fish oil are possible options. Orexigenic agents may be prescribed if patients wish to improve oral intake. Steroids and progestational agents may be used to attempt to improve mood and appetite.

Nutrition affects symptoms that need to be managed effectively. Nurses should work aggressively to correct factors that contribute to decreased food intake (e.g., nausea, pain) and correct factors that worsen debility (e.g., anemia). Information must be presented so that informed choices can be made and realistic eating goals set. An interdisciplinary approach that involves the nurse, physician, dietician, and possibly social worker or case manager, as well as the patient and family, is necessary to identify nutritional alterations, assess specific needs, and plan individual interventions. Whitman (2000) stated that counseling is the most effective and least expensive intervention. It may be conducted by any member of the healthcare team and should be combined with other interventions. Palliation of cachexia in patients with advanced cancer is a challenge for nurses. Hopefully, early and judicious use of these interventions may decrease the significant morbidity and mortality that result from cancer cachexia.

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References


For additional discussion of cachexia, see “From Research to Clinical Practice” on p. 241.