Palliative Management of the Patient With Advanced Pancreatic Cancer

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For the patient with advanced pancreatic cancer, curative strategies may not be appropriate, and palliative symptom management may be the best approach to patient care. Oncologists,

Introduction

In the United States, the care of cancer patients is a critical issue that impacts on both the medical community and society in general. The scope of this issue continues to expand due to a number of factors, including the aging of the US population and the increasing incidence of specific cancers.

It has been estimated that in 1996, 1,359,150 people will be diagnosed with cancer in the United States and 554,740 will die of this disease [1]. Thus, despite the continuing emergence of new cancer therapies, about half of all cancer patients will die of their disease. This suggests that many patients with advanced cancer will require treatment strategies focusing on symptom management, because curative strategies may not benefit them [2]. This approach will require a shift in the focus of cancer research to include studies of palliative treatment in addition to new curative regimens. Oncologists, who have been trained to concentrate on curing cancer, will be required to integrate palliative treatment strategies into patient management. These changes are likely to be affected by the increasing role of health economics in the treatment decision-making process [3].

Issues Associated with Palliative Therapy

Challenges for the Oncologist

Current approaches to palliative treatment for patients with advanced cancer are fraught with deficiencies [4]. Many physicians fail to appreciate the impact of symptoms on the patient's quality of life or may lack an understanding of how to treat the whole patient rather than just the tumor. These problems reflect a void in the oncology training curriculum [2,5]. For example, although pain is a dominant cancer symptom, pain control has only recently been included in the Medical Oncology Board examinations [4]. Furthermore, uniform clinical practice protocols for palliative treatment are lacking. Although some institutions have begun to develop these protocols, most cancer centers have not instituted systematic approaches to palliative patient management [2]. For a list of the most common symptoms in advanced cancer patients, see Table 1 [6].

Due to the aging of the US population, oncologists will be increasingly faced with managing cancer patients who have a variety of other age-associated illnesses, including osteoarthritis, diabetes, and congestive heart failure. Oncologists will require training not only in the appropriate use of palliative treatment regimens but also in the treatment of patients with advanced cancer who have multiple diseases and associated symptoms. Overall, the clinical role of the oncologist must encompass preventive oncology, diagnostic evaluation, communication, antitumor therapies, symptom control, optimization of social supports, and care of the dying patient [2].

Measuring the Efficacy of Palliative Interventions

Measuring tumor response is a well-established means of determining the efficacy of cancer therapy. Unfortunately, there is no gold standard quality-of-life measurement to assess the efficacy of palliative interventions. Various tools have been developed to permit the systematic, reproducible assessment of patients' quality of life (Table 2) [7]. Although these assessment tools can provide useful information for the oncology researcher, the implementation of these tools in clinical practice has been difficult. For example, the instrument may not ask questions specific to the patient's particular cancer, or it may be too detailed for the patient [6]. Thus, at present, the practicing oncologist should rely on communication with patients to determine the efficacy of palliative treatment regimens.
Palliative Management of Advanced Pancreatic Cancer

While palliative interventions should be considered for all patients with advanced cancer, advanced pancreatic cancer provides a distinct challenge for the oncologist. The nonspecific and vague symptoms associated with pancreatic cancer contribute to a delay in diagnosis, and most patients are diagnosed at an advanced stage [8,9]. In its advanced stages, pancreatic cancer is associated with a plethora of symptoms that require treatment. In addition, a small number of patients have histories of substance abuse that must be considered, but this does not preclude adequate palliation [10,11].

Complications and Symptoms
The most common symptom associated with pancreatic cancer is pain, which occurs in approximately 80% of patients [6,12]. Other symptoms include anorexia, early satiety, xerostomia, sleep problems, weight loss, fatigue, weakness, nausea, and constipation. In addition to these symptoms, physical findings may include cachexia, a palpable abdominal mass, ascites, and jaundice. Metastasis to other major organs, such as the liver, lungs, lymph nodes, and bone, also can occur [12].

Pain Management
According to the World Health Organization, 20% to 50% of patients with cancer present with pain, approximately 33% experience pain during treatment of their disease, and 75% to 90% of patients with advanced or terminal cancer have pain [13]. The reasons for this problem include societal barriers due to the perceived potential for misuse of opioid analgesics, insufficient knowledge about pain control measures among health-care providers, governmental regulations, and health economics [4,14]. Physicians face a variety of obstacles when treating the patient with cancer pain, including complications from the side effects of other medications; metabolic abnormalities, such as liver dysfunction; and homebound patients with rapidly changing disease [15]. A critical component of pain management is communication and trust between the physician and the patient [16]. For the patient with advanced cancer, the goals of pain management should be to permit an acceptable level of functioning and to allow the patient to die as free of pain as possible [16]. Therapeutic options to treat cancer pain include behavior modification, standard drug therapy, experimental drugs or novel methods of drug administration, and selective anesthetic and neurosurgical approaches.

General Guidelines for Using Analgesics--Analgesic drugs can be divided into three categories: nonnarcotic analgesics (ie, aspirin, acetaminophen, nonsteroidal anti-inflammatory drugs) that act on peripheral pain mechanisms; narcotic agonist and antagonist drugs that interact with opiate receptors (morphine, hydromorphone, methadone, levorphanol, oxymorphone, heroin, codeine, oxycodone); and adjuvant analgesic drugs that produce analgesia in certain pain states or potentiate opioid analgesics [16]. Unlike nonnarcotic analgesics, the dose-response relationship of opioid agonists is logarithmic, such that the increment in analgesia is linear until loss of consciousness [17]. Unfortunately, many physicians underuse opioids to treat cancer pain, probably because of controlled substance regulations and/or concerns about sedation, respiratory depression, tolerance, and addiction [11,18].

The optimal use of opioid analgesics requires maintaining a balance between their benefits and toxicities. Side effects may include nausea, vomiting, mental clouding, sedation, constipation, urinary retention, and pruritus. Appropriate strategies to manage these side effects should be anticipated for patients on opioids. Furthermore, since opioids produce different responses in different individuals, the analgesic regimen must be tailored to the patient's response, in terms of both the drug's analgesic efficacy and its side effects. It is important to note that it is rare for patients with cancer pain to develop psychological dependence on these drugs [16].

Guidelines for Using Opioids in Pancreatic Cancer Patients--Pain management in patients with pancreatic cancer is notoriously difficult. There is a history of alcohol and/or benzodiazepine abuse in a significant number of these patients. Because of this, their tolerance to analgesic dosing is higher than in the typical cancer patient, and the prescriber must be prepared to use higher doses of analgesics than in patients with other common solid tumors. No specific opiate appears to have superior activity in the setting of pain related to pancreatic cancer. The principles and practice of opiate use in this setting are similar to those in other situations, with one exception: There is a much higher risk of small bowel obstruction in patients with pancreatic cancer. Opiate-induced bowel obstruction is a preventable complication in this setting, but patients and their families must be warned specifically to watch for symptoms suggestive of bowel obstruction and to call the physician immediately should these be noted. Also, aggressive use
of laxatives is essential to prevent this complication. A specific technique that is invaluable in patients with pancreatic cancer is the continuous administration of subcutaneous opiate infusions by means of a patient-controlled analgesia (PCA) pump. This approach has the advantage of delivering analgesics reliably in patients who have impaired gastrointestinal function and for whom oral analgesics may not be the best choice. In addition, in patients who develop a bowel obstruction, a PCA pump can ensure optimal analgesia despite their inability to take liquids or food by mouth.

**Management of Bowel Obstruction**

Bowel obstruction can be caused by extrinsic bowel compression from the primary tumor or from intra-abdominal, intraluminal, or intramural metastases; postirradiation or postoperative fibrosis; mesenteric ischemia; or neurogenic, metabolic, or drug-related causes. The differential diagnosis includes constipation, as well as other benign or malignant conditions [19]. Bowel obstruction is diagnosed by the symptoms of pain, nausea, vomiting, and abdominal distention in addition to a characteristic appearance on x-rays [20]. Surgery may be a treatment option [19]. Other treatment strategies may include IV fluids, nasogastric suction and discontinuation of stimulant laxatives, and drugs that increase peristalsis. Effective management of established bowel obstruction can be achieved in many patients using subcutaneous opioids, antiemetics, and octreotide (Sandostatin).

Immediate management in a patient with an established bowel obstruction should focus on control of pain and associated nausea and vomiting. Pain control is usually not a problem. The exception to this is the development of severe abdominal cramping, which may respond to anticholinergic agents. **Nasogastric suction** is an important early step in patients with large-volume emesis. If there is no large-volume emesis, nasogastric suction is not indicated. **Intravenous fluids** are employed to maintain hydration and, hopefully, to allow that patient to recover from the bowel obstruction. Unfortunately, in patients with advanced disease this does not often occur because frequently there are obstructions on multiple levels. In this setting, withdrawing the nasogastric tube and allowing the patient to eat and drink small amounts as required is the most humane course. **Octreotide** has been a significant advance in treating patients with bowel obstruction, as it reduces intestinal secretions and may allow nasogastric suction to be discontinued. The dose of octreotide is titrated to control the volume of secretions. Octreotide has the advantage of being able to be administered subcutaneously for long-term use and also can be mixed with other medications for continuous subcutaneous infusion.

**Laxatives and Prokinetic Agents**-- The role of laxatives and prokinetic agents in this area is controversial. Suffice it to say that stimulant laxatives that cause smooth muscle spasm, eg, bisacodyl, should be avoided since they tend to increase abdominal pain due to their mode of action. In patients with incompletely established bowel obstruction, there may be a role for prokinetic agents such as metoclopramide or cisapride (Propulsid), but the outcome of introducing these agents needs to be carefully assessed. In patients with fully established bowel obstruction prokinetic agents have no role. In a minority of patients, aggressive use of laxatives and enemas to empty the lower bowel will resolve a bowel obstruction. This approach should be pursued vigorously until it is clear that the bowel is permanently obstructed.

**Management of Anorexia, Early Satiety, and Cachexia**

The management of anorexia, early satiety, and cachexia may include nutritional and pharmacologic interventions. The goal of nutritional support is to alleviate hunger, reduce anxiety about starvation, and preserve the important social aspects of mealtimes [21]. No benefit has been associated with the force-feeding of meals or the consumption of high-calorie oral preparations. However, patients may benefit from small, frequent meals or enteral nutritional supplements. The use of parenteral nutrition is controversial due to the high risk of complications, high cost, and lack of proven benefit [21]. Pharmacologic interventions to manage anorexia include the use of metoclopramide, megestrol acetate, corticosteroids, and cannabinoids, among other agents [4,21].

**Management of Nausea and Vomiting**

The first step in treating the patient with nausea and vomiting is to pinpoint their cause. If the cause cannot be determined, general measures for alleviating these conditions are applied. For many patients, nausea and vomiting can be managed with antiemetics, which block neurotransmitters that conduct emetic stimuli [22]. Since most patients also experience early satiety, metoclopramide, administered either orally or intravenously, is the drug of choice for routine use. Nausea and vomiting may also be managed with oral, rectal, or IV prochlorperazine or 5-hydroxy-tryptamine-3 antagonists.
antiemetics such as ondansetron (Zofran) and granisetron (Kytril) [23-25]. Both haloperidol and dexamethasone are invaluable for patients who are unresponsive to a phenothiazine and/or metoclopramide.

Management of Constipation
The cause of constipation may be physiologic, pharmacologic, metabolic, neurologic, or structural (Table 3) [26]. A careful bowel history and abdominal examination usually reveal the cause of constipation. At our center, we routinely use the stool softener docusate sodium, given three times daily supplemented by magnesium hydroxide. For severe cases, rectal suppositories, osmotic agents (such as sorbitol and lactulose), and disimpactions may be necessary [20]; suppositories may be precluded if the patient has neutropenia or thrombocytopenia.

Management of Diarrhea
Diarrhea has been reported in up to 18% of patients with pancreatic cancer, depending on the location of the tumor. A higher incidence of diarrhea is associated with tumors in the head of the pancreas than with tumors in the body and tail [9]. Appropriate management of diarrhea depends on identifying the cause. Diarrhea may result from the tumor itself, treatment of the malignancy, infection, or metabolic abnormalities [27]. Malabsorption with steatorrhea is common, and lactose intolerance may also be seen. After the cause is identified, an appropriate management plan can be developed. In general, diarrhea associated with pancreatic insufficiency can be treated with high-calorie protein and carbohydrate diets and replacement of pancreatic enzymes. Various enzyme preparations are available.

Management of Ascites
The incidence of ascites, like that of diarrhea, depends on the location of the tumor [9]. Frequently, abdominal fluid collection and abdominal distention are indications of metastatic disease in patients with pancreatic cancer [28]. Treatment of malignant ascites is directed at the underlying cancer. The management of ascites in the setting of cancer is difficult but symptomatic control is possible in selected patients with the judicious use of diuretics.

Diuretics--In many patients, symptoms of ascites can be well controlled with the combination of spironolactone and furosemide. Conventional doses of these agents can significantly reduce ascites, improve patient comfort, and obviate the need for repeated paracentesis. Careful monitoring of the patient's blood pressure (lying and standing), amount of edema on clinical examination, and serum sodium level will allow an appropriate balance of diuresis to be achieved.

Paracentesis in the cancer patient can be used to remove large volumes of liquid without impairing renal function, although this should be performed with caution in those with preexisting renal impairment or those with other illnesses associated with cardiovascular instability. Frequent paracentesis should be done only in patients who have tense ascites and significant associated symptoms, as experience suggests that frequent paracentesis is also accompanied by rapid return of the ascitic fluid.

Management of Dyspnea
Dyspnea may occur with all primary-site cancers, even in the absence of cardiac or pulmonary disease. In pancreatic cancer patients, the incidence of dyspnea is approximately 20%, and patients who are dyspneic have a shorter survival than those who are not [12]. The successful management of dyspnea in patients with advanced cancer requires comprehensive evaluation and treatment, since it is a subjective complaint that is often multifactorial and may not be directly related to the cancer, but rather, may be caused by treatment of the tumor or disease complications. Specific interventions for dyspnea in advanced cancer patients are summarized in Table 4 [29].

Hospice Care and Palliative Care Centers
Approximately half of the 500,000 cancer patients who die each year are cared for by 1 of the 1,700 hospice services developed in the last 2 decades [4]. These centers employ a multidisciplinary approach that focuses on symptom management rather than on prolongation of life [30]. One major drawback of hospice organizations is that they are usually separated from acute medical care facilities.

In contrast to hospice centers, palliative care centers were designed to integrate the philosophies and practices of a hospice into a medical center. These centers are still unusual. The Cleveland Clinic Palliative Care Program originated in 1987 through the creation of an inpatient consultation service [31]. The program was designed to help relieve patients' pain and other symptoms and to provide...
psychological and spiritual support for the patient and family. Subsequently, an outpatient clinic, a research program, a community board of advisors, a hospice home-care service, a cancer home-care service, and a dedicated inpatient unit were added.

**Conclusions**

For patients with advanced pancreatic cancer, palliative management of symptoms is often the best approach to patient care. These patients are multisymptomatic and often require treatment for such conditions as pain, bowel obstruction, anorexia, early satiety, cachexia, nausea and vomiting, constipation, diarrhea, ascites, and dyspnea. To optimize treatment of these patients, physicians must be trained in the relevant therapeutic strategies. In addition, the development of special palliative care programs will accomplish both comprehensive patient care and continued research and education in this important area.

**References:**


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