



Pierre-Auguste Renoir. *Roses*, 1890.

The principal role of the clinician for patients with advanced pancreatic cancer is to manage progressive symptoms and relieve pain and suffering.

Palliative Care in Pancreatic Cancer

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Background: Pancreatic cancer is a formidable health problem, representing the 10th most common malignancy in the United States and the 4th most common cause of all cancer deaths. The overall 5-year survival rate is 4%, making this disease a model tumor in which to address the specialized care issues of palliative medicine.

Methods: General considerations in both medical decision-making and symptom management are reviewed. Treatment of patients with locally unresectable, recurrent, or metastatic disease is individualized, based on considerations that include patient age, patient wishes, family influence, insurance constraints, and geographic practice variations.

Results: Success in managing progressive symptoms is needed to palliate patients with advanced pancreatic cancer. Common problems include biliary obstruction, depression, pain, intestinal obstruction, and fatigue.

Conclusions: Relief of pain and suffering associated with critical illness is required in managing patients with cancer. Pancreatic cancer is a model illness that mandates this need.

Introduction

Pancreatic cancer is a formidable health problem with increasing incidence.¹ Although this tumor represents only 2% of new cancer diagnoses in both men and women and is the 10th most common malignancy in the United States, it is the fourth most common cause of all cancer deaths. Despite advances in the understanding of the

pathology and biology of the disease, as well as improved diagnostic imaging and staging studies, the overall 5-year survival rate remains 4% for all stages and races.

Adenocarcinoma of the pancreas comprises 90% to 95% of all malignant tumors of the exocrine pancreas. It is one of the most lethal malignancies, and its geographic location within the body makes imaging studies and biopsy procedures more difficult compared with other tumors. There are no clear-cut high-risk populations to follow, even if effective screening procedures were available. More problematic is the reality that presenting symptoms are vague, diverse, and long-evolving before medical attention is sought.

The clinical presentation is often dramatic, with “painless” obstructive jaundice. There is often a history of mild but progressive discomfort or pain in the mid-abdomen, occasionally with radiation to the back, and usually noted worse at the end of the day.

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Submitted July 8, 2003; accepted December 15, 2003.

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Ten percent of patients have a new onset of diabetes. Others describe fatigue, anorexia, nonspecific gastrointestinal symptoms, weight loss, and depressed mood — all of which can go unnoticed until there is an obvious need to seek medical care. Patients may require symptom relief before any treatment interventions can begin, and some patients move rapidly to a state where the options are aimed solely at comfort. Multiple complaints, poor performance status, and comorbid illness make definitive surgery a less likely option. Interestingly, long-standing symptoms, weight loss, and anemia are not negative predictors of survival by univariate analysis, if the patient is able to undergo a resection.² In a series of 13,560 patients with pancreatic cancer, a major predictor of survival was the ability to undergo a complete resection, whereby survival rates were 2-fold greater compared with palliative bypass procedures.³ Yeo et al⁴ reported that residual disease, manifested by positive vs negative margins, translates into a 5-year survival rate of 8% vs 26%. This disease is a model tumor to address the specialized care issues of supportive and palliative medicine.

Decision-Making: General Considerations

Although unresectability represents the poorest prognostic factor, even patients who are able to have a Whipple procedure with clear margins often relapse, making this one of the most biologically aggressive cancers. Management of the minority of patients intended for curative resection usually causes little controversy. However, those with locally unresectable, recurrent, or metastatic disease generate additional issues that go beyond the pure medical picture: patient age, patient wishes, family influence, insurance constraints, and geographic practice variations.

There is an increasing mandate in oncology to improve outcomes, to limit adverse events, to control escalating costs, and to improve patient satisfaction. These are meaningful goals that drive a treatment approach for an illness that has a 5-year mortality rate of 95%. Half of patients may be too ill for entrance into a clinical trial, and the remaining half may not qualify because of age, nonmeasurable disease, serious comorbid illness, or a second malignancy.⁵ In many cases, because of patient and/or family insistence, patients with poor performance are given chemotherapy outside of a clinical study, sometimes with a minimally toxic regimen. Many patients are never considered for hospice programs or are referred late for end-of-life care. This occurs for a variety of practical reasons: (1) Some patients and/or their family members refuse to accept a noncurative, nonaggressive approach. One study showed that 53% of cancer patients were willing to accept intensive chemotherapy and endure toxicity for a 1% cure rate. More than 40% would do the same to extend their lives by 3 months.⁶ (2) Some

patients may be good candidates for a clinical trial. (3) Physicians feel the need to instill a level of hope. (4) Financial incentives may affect behavior of some treatment teams. (5) Some patients distrust all conventional medical care, including hospice, and choose an alternative or complimentary medicine approach.

Success in managing the complex, multiple, progressive signs and symptoms in pancreatic cancer is important for all patients at all stages of disease, but this becomes the overriding imperative for those facing advanced illness. Even with treatment, most gastrointestinal cancers still fail to show complete tumor regression, and despite obvious responses, meaningful survival benefit may be modest. The oncology literature now recognizes the importance of symptom control measures and supportive services that diminish the unacceptable side effects of beneficial anti-cancer therapies such as antiemetics, erythropoietin, colony-stimulating growth factors, and antibiotics.⁷ However, at times, efforts to manage symptom progression are addressed by escalating intensity or prolonging treatment regimens rather than by comforting patients whose tumors are truly failing to respond.⁸

The clinical ability to effectively relieve a patient's distress begins with an understanding of the natural history of the tumor as well as the biological behavior or tempo of progression. This knowledge allows the treatment team to anticipate and manage the changing picture of the clinical presentation. Consideration of the patient's age, comorbid problems, functional status, mental capacity, preferences, and previous responses to adequate clinical trials all help to clarify the potential outcome and the aggressiveness of further therapy. The following considerations may be useful in the decision-making process for patients with malignancies:

- Establish with reasonable certainty the extent of disease and whether the cancer is beyond curative therapeutic intervention. Is the tumor resectable?
- Evaluate the etiology and severity of symptoms and relate them to the pace of progression and extent of disease. Inexperienced physicians may be less critical in their clinical assessment, sacrificing useful options that may produce meaningful tumor responses and reduce intensity of symptoms.
- Determine if the patient's signs and symptoms are compatible with the natural history of pancreatic cancer. It is wise to rule out treatable noncancer causes, such as pulmonary embolus, and to recognize and manage problems related to the treatment itself. Pancreatic cancer is generally a disease of older individuals — the mean age of onset is 65 years, with 80% of patients 60 years or older. Many of these patients have concurrent morbidities and use several medications, which may confusion to the clinical picture.

- What potential limitations of function are imposed on the patients due to the disease, diagnostic intervention, or treatment? Early pancreatic cancer is not easy to diagnose. Computed tomographic or magnetic resonance imaging scans are often not definitive, so further diagnostic studies that include fine-needle aspiration and endoscopic retrograde cannulation of the pancreatic duct (ERCP) may be indicated.
- What information needs to be communicated to the patient, family, and other members of the treatment team? How much is clearly understood? Are there elements of denial or unrealistic expectations driving treatment decisions that may be inappropriate?
- What are the management goals for this patient? These will change over time. Is further chemotherapy futile? The meaning of futility may need to be defined for specific objectives (eg, survival, function, pain, satisfaction, and quality of life). Here, the patient's goals and expectations become of paramount importance.
- What other options and recommendations can be offered if the patient refuses the clinician's plan of therapy?

Most oncologists understand the distinction between therapy for curative results and therapy for end-of-life care. The challenge is determining whether further palliative treatment remains valid as disease progresses. There is no benefit to continue anticancer treatment that fails to prolong life, improve functional limitations, or reduce symptoms of illness. At this point, management measures should focus on pain and symptom distress. The medical oncologist should know not only when interventions are indicated, but also when they are not.⁹ Some have suggested that we need to redefine anticancer medications to include those modalities that enhance patient well-being.¹⁰ Indeed, the use of gemcitabine in this disease is more valuable for palliating symptoms than extending survival!

For patients with advanced cancer, the manner and process of delivering medical care, as well as the possible outcomes, are intimately woven and connected. On the other hand, physicians may experience feelings of suffering, uselessness, loneliness, disappointment, and failure when treating dying patients.¹¹ Clinicians have a heightened, uncomfortable awareness of their own human frailty, vulnerability, and mortality. Factors that exacerbate this physician distress include inadequate training, fear of dying, poor communication skills, conflicts in goals of care, unrealistic expectations, and uncertainty of treatment outcomes.

Patients and physicians often disagree about qualitative and quantitative thresholds for futility.¹² Physician responses to futility cut-off points (ie, a chance of success)

varied from 0% to 60%, with a median and mode of 5%. Almost one fifth of physicians chose a threshold point of 20% or higher, while 4% of those surveyed were willing to have a cut-off point (for example, no further active therapy at 50%).¹² This lack of consensus shows a wide inter-individual difference among clinicians to define futile interventions and outcome measures. However, the variations in response may reflect only the differences among clinicians rather than differences in specific clinical scenarios.

Patients usually wish to avoid an experimental or risky procedure if the probable outcome of a standard treatment is in their perceived range of benefit. As expected, patients will be risk-takers for a novel approach when the known outcome of standard care is not in their favor.¹³ More problematic for patients as well as their physicians is the ability to access overwhelming information, some of which is based on media hype of "promising" therapies.¹⁴ It would be helpful if the practice of asking patients to choose between the options of only palliative care or anti-cancer therapy was discontinued in order to make both simultaneous supportive care and chemotherapy part of "best care." Pilot demonstration programs to address the feasibility of such a model of care have been reported.¹⁵

Predicting Survival and Prognosis

The ability to predict with accuracy the life expectancy of an individual with cancer is difficult, even among experienced oncologists.¹⁶⁻¹⁸ Oncologists have an obligation to be honest while still cultivating their implied promise of delivering hope to their patients. In the case of *Arato v Avedon* (Cal. 1993, 858 P.2d 598), a patient's family sued the attending oncologist for violating California's Informed Consent Doctrine. They claimed the patient was not told that 95% of people with his diagnosis and stage of pancreatic cancer would die within 5 years. The family argued that if the patient knew the facts, he would have elected to die "at peace" without experimental therapy. The physician countered that the patient was anxious and thus a detailed disclosure of such poor prognostic information was inappropriate to share with him. The Supreme Court of California agreed with the physician and claimed "...we believe it unwise to require as a matter of law that a particular species of information be disclosed." In a survey of oncologists on this matter, all believed that giving hope was a necessary goal of their profession.¹⁹ Kodish and Post²⁰ reported that patients expect clinicians to disclose information after some interpretation of the data, but they do not want "callous disclosure of grim diagnosis and prognosis." Patients need to appreciate that the whole range of possibilities for their particular cancer may not follow a set course and in fact may be better or worse than the probabilities show.

This obligation of physicians to nourish their patients' hope — to see some good to their future — remains a challenge. Lamont and Christakis²¹ have shown that physi-

cians usually make optimistic errors in foreseeing patient life expectancy, and they make larger conscious optimistic errors in the actual disclosure to patients as to their survival time. Christakis²² further reports that “it is important to realize that physicians often believe that prognostication is itself intrinsically and fundamentally a lie...any statement about it — but especially one that might be construed as definitive — is seen as necessarily mendacious.” Physicians regard this as a “considered use” of information rather than a “deliberate distortion” of information and thus see no conflict between presenting an optimistic picture and their need to be truthful.

Symptom Control and Palliation

Despite clinicians’ mandate to comfort their patients, the current practice of medicine to relieve suffering is “more a hope than standard” for most patients.²³ Forty percent will die with unrelieved pain,²⁴ and 50% of hospitalized terminally ill patients have pain that is ignored by their caregivers.²⁵ Physicians and nurses tend to minimize their assessment of pain, especially when patients describe significant pain.²⁶

Treatment planning for patients with pancreatic cancer usually includes measures that aim at simultaneous tumor response and symptom management. Because curative outcomes or long-term remissions are not likely to occur in a disease so biologically aggressive, the challenge to integrate hope, treat the cancer aggressively, and simultaneously face reality becomes a frustrating and difficult experience for the clinician.

Biliary Obstruction

Since 70% to 85% of patients have tumors involving the pancreatic head, the development of jaundice is a common initial presentation. Most patients have a previous history of unsuspecting vague, nonspecific abdominal discomfort that predates the jaundice. Biliary obstruction may occur later in the illness due to growth of an unresected primary tumor, recurrent tumor, enlarged regional nodes, or biliary stent occlusion. Ninety percent of patients will have jaundice at some time in their illness, with associated symptoms of malaise, pruritus, loss of appetite, fever, and abdominal discomfort. The optimal strategy for treatment may not be initially obvious due to the patient’s age, life expectancy, and generally poor well-being, or the physician’s experience and expertise. Biliary bypass surgery has long been utilized for patients with unresectable disease or, in cases where other options are unavailable, for relieving disturbing symptoms and perhaps prolonging patient survival.²⁷

Endoscopic placement of Teflon stents, introduced in the 1980s, is now routinely performed with a 90% success

rate, with the majority successfully placed during the first procedure. However, plastic endoprotheses require changing at 3 to 6 months because of occlusion and a return of jaundice, fever, and discomfort. It is unclear whether antibiotics or bile salts help stents to remain patent.²⁸ The placement of a metal stent in a patient with repeated bouts of cholangitis is also controversial. The stent can become blocked by tumor invasion without prolonging survival.²⁹ However, the relief offered by stent placement may enhance the patient’s overall quality of life, even in a population of individuals whose survival is limited.

Depression

It has long been known that depression is more common in patients with pancreatic cancer than in those with other malignancies. A well-described study of 139 patients who were admitted for possible colon or pancreatic cancer reported that 76% of patients with pancreatic cancer had depressive symptoms prior to surgery compared to 17% of patients with colon cancer.³⁰ A small National Cancer Institute study also revealed major depressive symptoms in half of the patients with pancreatic cancer compared with none in patients with gastric cancer.³¹ A large literature of retrospective reviews has tried to connect the issue of unrelieved pain and misdiagnosis to depressive symptoms in this illness.³² Foley³³ noted that pain was a presenting symptom in 80% of patients and occurred sometime in their illness in 90% of patients. Because of the widely held belief that pain and depression are common with pancreatic cancer, Kelsen et al³⁴ prospectively evaluated these symptoms in 130 newly diagnosed patients: 83 patients prior to a surgical procedure and 47 before their first chemotherapy treatment. All patients had excellent performance status and were being treated at a major tertiary cancer center. The Beck Depression Inventory (BDI) and Beck Hopelessness Scale (BHS) were utilized, as well as other validated tools, to measure pain and symptom distress. Only 29% of these patients complained of moderate to severe pain. The patients receiving chemotherapy reported more pain than did preoperative patients. BDI scores were ≥ 15 in 38%, suggesting high levels of depressive symptoms. There was a strong correlation between increasing pain and depressive symptoms among those with pain. However, the authors concluded that moderate or severe pain and symptoms of depression were less prevalent than originally thought. This study examined patients earlier in their disease where severity of depression and pain would be less prevalent. The patients receiving chemotherapy who were more likely to be depressed may have seen themselves as less likely to be cured. It is difficult to be sure since the number of cases in this treatment arm was small.

Some data suggest that patients with a prior history of depression have a worse survival when cancer occurs than would be expected on the basis of their cancer diag-

nosis alone.³⁵ If prior depression affects life expectancy among patients with cancer, effective intervention should be studied to substantiate survival outcomes. Brief psychotherapy (ie, fewer than six sessions with a psychiatrist) and cognitive therapy appear to be beneficial for patients in a palliative setting by addressing depressive symptoms, anxiety, and adjustment of patients to their illness (D. Schuyler, MD, personal communication, 2003). Interestingly, there is evidence that depressive symptoms may abate in patients with pancreatic cancer when the malignancy has been surgically excised.³⁶

Pain

In a prospective study of 1,107 patients admitted to a palliative setting, approximately 44% of those with pancreatic cancer had severe pain.³⁷ Again, the prevalence of depressive disorders of all types were found to be higher in cancer patients with severe pain, raising an inference of causation. This link between pain and depression, along with anxiety, underscores the problem of undertreatment for pain as the most common opioid abuse issue in the care of the dying.³⁸

Pain is the aspect of cancer that is most worrisome to both patients and their families. Half of respondents to public surveys about pain believed physicians cannot make a difference and this fear translated to 20% claiming they would avoid seeking cancer treatment.³⁹ The paradox of cancer pain is the following: it is the most feared symptom, the most connected and interwoven to other cancer symptoms (insomnia, fatigue, nausea, constipation), and yet the most treatable of cancer complaints. Oral analgesics provide relief to 90% of patients with cancer.⁴⁰

Pain syndromes with pancreatic cancer can occur due to the proximity of the organ to a number of other critical structures: the duodenum, liver, stomach, jejunum, and transverse colon. The pancreas itself is innervated by nerve networks that interact with both the parasympathetic and sympathetic systems. Pain may be felt at multiple and distant sites. Discomfort arising from the body of the pancreas appears as midepigastic discomfort, while pain coming from the tail is often localized in the left epigastrium and left intercostal space. Obstructive symptoms are cramps, poorly localized with a crescendo-decrescendo quality, while destruction of pancreatic tissue itself causes further inflammation and discomfort. Pain can be referred to somatic structures without tumor infiltration of somatic nerves. The pain is progressive, and its character, quality, and temporal nature worsen as the illness progresses. The liver is a common site of metastasis, and pain can arise due to nociceptive sensitive areas located within the liver capsule and biliary tract. Pain can be referred to the right shoulder or neck.

Most patients with chronic malignant pain will require an opioid regimen consisting of around-the-clock dosing,

with a “rescue” dose calculated at approximately 15% of the 24-hour baseline dose. Oral doses may need to be given every hour for relief, and the severity of the pain will determine the dose, route, and frequency of the analgesic intervention. Finding the correct opioid may be empirical, ie, trial and error. Common reasons for inadequate pain control include making errors in dosing, failing to escalate total and breakthrough dose, not addressing side effects, and not using alternative opioids and adjuvant analgesics (eg, antidepressants, anticonvulsants, corticosteroids).

Patients with rapidly advancing illness present special problems, and progressive cancer is a major reason for increasing opioid dosage.

The final opioid dose required for relief is the dose that works with an acceptable side effect profile. The dosing requirements necessary to deliver adequate pain relief vary widely among patients. For example, at our center, nearly one third of patients with pancreatic cancer require a 48-hour dosing schedule with transdermal fentanyl patches. The development of tolerance is not an important issue when dose escalation is required. Patients quickly become tolerant to the side effects of respiratory depression, nausea, and sedation, but do not become tolerant of constipation.

Percutaneous celiac plexus blockage can be a beneficial adjunctive interventional technique in individuals whose pain is poorly controlled with opioids and who are bothered by escalating adverse effects. In most cases, analgesic responses are high (>50%) with a wide range of duration.⁴¹ No controlled trials have been conducted in which conventional pain management is compared to neurolytic intervention. Complications are usually mild, but in rare cases the procedure can cause significant complications, including pneumothorax, paraplegia, and ischemic gangrene of the bowel. In some centers, the procedure is now recommended as the first approach to pain, followed by the titration and escalation of opioid analgesia.

Intraspinal drug delivery (intrathecal or epidural) also can be effective in selected patients with intolerable abdominal cancer pain.⁴² Smith and colleagues⁴³ recently reported the value of an implantable drug delivery system in a randomized clinical trial, which also reported a survival benefit in patients with refractory cancer pain.

Radiotherapy in pancreatic cancer is principally used as a palliative modality. There are no controlled randomized trials to evaluate the impact on pain with other pain therapies, such as celiac plexus block or the use of opioids alone. However, in patients with advanced local disease, radiation is often considered to manage pain.

Intestinal Obstruction

Despite the fact that less than 5% of patients present with duodenal obstruction until late in the course of illness (often a preterminal event), obstruction can manifest any-

where in the gastrointestinal tract. A thorough history and physical examination is essential to assess etiology and define treatment options. Many patients have progressing tumor with associated poor performance, immobility, and dehydration, and they are taking opioids for pain. The differential diagnosis must include concerns of obvious progression of the cancer, decreased bowel motility, ileus, opioid-induced nausea, and constipation. Nasogastric suctioning and fluid replacement often relieves the situation, at least temporarily. Surgical intervention is usually not considered because these patients are poor surgical risks and often have widespread intra-abdominal disease with multiple points of obstruction. Medical management can be difficult, and treatment decisions depend on the age of the patient, past treatments, and closeness to death. Pharmacologic agents can include dexamethasone, haloperidol, and octreotide, which have been helpful to some with intestinal obstruction, nausea, and increased intestinal secretions.⁴⁴⁻⁴⁶ Aggressive nutritional support with total parenteral nutrition is reserved for patients whose survival and quality of life might be enhanced by active anticancer therapy. No data are available to support its use in patients with advanced disease. The decision to continue active support may be influenced by patient or family pressure, but most often this is not the case, and care at the end of the life can be maintained at home even without intravenous fluids for those obviously near death. Radiation and chemotherapy offer little help, especially since in most cases, disease has progressed despite utilizing these modalities weeks or months before.

Expandable metal stents may be helpful in desperate nonsurgical candidates. Advanced pancreatic cancer of the pancreatic head can commonly obstruct the gastric outlet. Approximately 90% of patients with gastroduodenal stents improve clinically, and oral intake can resume quickly.⁴⁷ Endoscopic placement allows the stent to reach the obstruction directly with relief to the proximal jejunum. Complications include perforation, bleeding, stent migration malposition, and failure due to tumor overgrowth and blockage.

Fatigue

Fatigue is the most common symptom in patients with cancer.⁴⁸ Cancer-related fatigue is a subjective experience that has a detrimental influence on the patient's quality of life, diminishing physical, emotional, work, and social relationships. The pervasive extensions of profound malaise can alter patients' ability to retain information and to continue with their treatment programs, thus lessening their success of achieving an antitumor response. The magnitude of the problem of fatigue has been underestimated, and there are no validated animal models to study, as there are with pain. Ninety per cent of patients' loved ones

reported observing fatigue, and oncologists described 76% of their patients with this complaint.⁴⁹ The pathogenesis of cancer-related fatigue is unknown and may represent a final common pathway for multiple possible mechanisms. Several possible contributing factors can be identified in patients with pancreatic cancer: depression, pain, opioid use, anemia, chemotherapy with or without radiation, insomnia, dehydration, and cachexia. The abnormal production and distribution of cytokines may be other possible mechanisms, as they have been implicated in the chronic fatigue syndrome.⁵⁰ Treatment is often difficult and focused on obvious factors that are correctable: pain, anemia, insomnia, depression, and dehydration.

Terminal Events

The dying process — the final phase of any illness — can be overwhelming for both patient and family. Difficulties with this process can be accentuated by clinicians' confusion, indifference, negligence, and frank abandonment. Observing the last hours of 200 consecutive terminal patients in a quiet hospice setting revealed that nearly 40% had a specific problem that required attention, but the majority (91%) were thought to die "peacefully," without signs of bleeding, hemoptysis, dyspnea, pain, restlessness, or regurgitation.⁵¹ Less than 10% of these patients were overtly confused, with nearly one third conscious until death and only 1% unresponsive for more than 48 hours prior to death.

It is rare for symptoms to be so unmanageable near death that total sedation is required to ease a patient's suffering. If sedation is necessary, several issues need to be addressed: (1) have a collaborative medical consultation, (2) communicate clearly with the family to understand the patient's wishes, (3) ensure that death is imminent, (4) ascertain that symptoms are progressive, severe, and refractory to treatment measures, (5) have clear goals and a plan (eg, no cardiopulmonary resuscitation), (6) establish good communication with non-physicians, particularly the nurses involved in care, and (7) maintain good documentation of the above recommendations.

There is always a moral imperative for medical care that provides comfort. Pancreatic cancer is a model illness that mandates this imperative. Physicians need to develop a better appreciation of the nature of their patients' distress beyond the physical nature of their symptoms. They must also recognize that the severity and chronicity of any specific complaint are interwoven with their patients' perception of their life quality and meaning. The patient's preparedness to die depends on what remains for that person to do and with the physical and mental capacity of that person to accomplish it. The compassionate and competent manner in which care is delivered at the end of life helps the sickest of our patients and their families to transcend suffering.

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