The Challenge of Palliating Pancreatic Cancer

March 15, 2013
By Mellar P. Davis, MD [1] and Pamela Gamier, RN [2]

FDA approval of palliative chemotherapy is largely based on disease-free and overall survival, quality of life, and symptom reduction; the latter should be routinely measured by the treating oncologist. Physician assessments of symptoms underreport symptom severity compared to patient-reported symptom assessments.

Drs. Torgerson and Wiebe have written a thorough and up-to-date article on supportive care in pancreatic cancer. Several additional comments may add to this excellent review.

Venous Thromboembolism (VTE)

Cancer-related thromboembolic disease has been recognized since Armand Trousseau’s original description in 1865.[1] Only recently have high-quality trials been undertaken to prevent thromboembolism in cancer patients. Many of the trials, however, do not take into account the heterogeneity of cancer or the heterogeneity of the causes of thromboembolism in cancer patients. There is an integral relationship between tissue factor expression, angiogenesis, coagulation factor VIIa activation, and tumor cell behavior—and this relationship may play a role in generating clots in patients with cancer.[2] This may be the reason for increased mortality associated with thromboembolism in pancreatic cancer.[3,4] Mucin production by pancreatic tumors may also be a predisposing factor.[5] Clinical factors are age, advanced disease stage, chemotherapy, and treatment with erythropoietin.[6] Heparins, both unfractionated (UFH) and low-molecular-weight (LMWH), as well as fondaparinux (Arixtra), have been shown to be effective in the prevention of VTE in patients with a history of cancer. Results of prophylactic heparin trials have been marginal since these have enrolled “all comers” during chemotherapy, yet only a minority develop thromboembolism and would benefit from anticoagulation.[7] UFH and LMWH, and semuloparin, have been used in a trial involving outpatients receiving chemotherapy. The number needed to treat has ranged between 33 and 50, so these agents have not become standard therapy.[8] Semuloparin has not been approved by the US Food and Drug Administration (FDA). Thus, the development of a risk profile—based on serum markers, tumor characteristics, and clinical characteristics—that could be used to define the phenotype of individuals at highest risk is an important priority. Another issue that should be addressed is how the benefits of the newer factor Xa inhibitors, for both prophylaxis and treatment of VTE, compare to those of heparins and vitamin K antagonists.[9]

Pain

The best timing and method for performing a celiac plexus block are not well defined. Neurolytic celiac plexus blocks can reduce pain from cancers arising anywhere from the distal esophagus to the transverse colon.[10] Blocks may be performed percutaneously, under CT guidance, or by way of gastrointestinal endoscopy with ultrasound guidance. Blocks have been performed using cryoablation with or without phenol and/or alcohol.[11] Neurolytic blocks have downstream benefits. Not only do celiac plexus blocks reduce constipation, but they may also reduce terminal delirium.[12]

The choice of opioids may be important. Most opioids cause spasms of the sphincter of Oddi. However, buprenorphine paradoxically decreases sphincter of Oddi contractions. Some experimental and single-arm studies have suggested that oxycodone is superior to morphine in reducing visceral pain severity.[13-15] However, this was not validated in a randomized trial.[16] There is some evidence that octreotide (Sandostatin) benefits patients undergoing endoscopic retrograde cholangiopancreatography (ERCP)-directed pancreatic duct stenting.[17] NSAIDs are quite effective in managing biliary colic and should be considered as first-line therapy for this condition.[18]

Stenting and Pruritus
Pruritus is a common symptom associated with cholestasis and is managed with stenting and bile acid binding agents. Pruritus occurs in 45% of patients with a biliary tract cancer; it involves the soles and palms and is characteristically worse at night.[19] Biliary draining via ERCP is still considered the first step for jaundiced patients when they present with cholangitis, intense pruritus, or severe jaundice. Stenting significantly improves emotional, cognitive, and global health scores. In addition to the expected improvement in pruritus and jaundice, improvement in anorexia, diarrhea, and sleep patterns have been reported.[20] Antihistamines are generally ineffective in reducing pruritus, as are gabapentin (Neurontin) and ondansetron (Zofran).[21,22] Met-enkephalin expression is increased with biliary stasis[23,24]; thus, the opioid antagonist naltrexone has been shown to reduce cholestatic pruritus.[25] First-, second-, third-, and fourth-line therapies are cholestyramine, rifampicin, naltrexone, and sertraline (Zoloft), respectively.[26] Animal models or anecdotal experience have suggested that cannabinoids, butorphanol (Stadol), low-dose propofol (Diprivan), molecular absorbent recirculation system therapy, and ultraviolet B phototherapy may be beneficial.[26]

**Cancer Anorexia and Cachexia**

Cancer anorexia is a syndrome of loss of appetite, early satiety, bloating, taste and smell changes, and diurnal alterations in food intake.[27] It is unlikely that a single drug will be able to treat the anorexia syndrome. However, certain symptoms may be targeted by specific drugs. Cannabinoids do not increase appetite in cancer, but are effective in palliating altered chemosensory perception.[28,29] Megestrol acetate has been the standard treatment for increasing appetite. However, a recent randomized trial demonstrated that olanzapine (Zyprexa) plus megestrol was superior to megestrol alone.[30] Anorexia frequently bothers families more than patients. Asking patients if they feel the symptom needs treatment is an important question to ask before increasing medication burden and cost. Family education, dietary counseling, and treatment of reversible causes of nutritional failure are the most important first steps in managing anorexia.[31] Cancer cachexia is classically defined by involuntary weight loss, and while it would seem simple to quantify, there is a great disparity as to the degree of weight loss that defines cachexia.[32] In addition to weight loss, cachexia is associated with selective lean body mass loss, fat atrophy, loss of function, and metabolic alterations (insulin resistance and hypertriglyceridemia). There are multiple ways of measuring body composition. The cost, availability, and invasiveness of measures such as anthropometric measurements, bioelectrical impedance, dual-energy x-ray absorptiometry (DEXA) scans, and CT scans will dictate their use. None of these have been standardized as routine measures.[32] Complicating the identification of cachexia is obesity, which is common in Western countries. The average pancreatic cancer patient undergoing palliative therapy is overweight. Sarcopenia in obese patients with advanced cancer is difficult to detect but has adverse prognostic outcomes.[33] Because of the multiple metabolic abnormalities associated with cancer anorexia/cachexia, (catabolism, blocked anabolism, and anorexia), multimodality therapy is needed, which includes orexigenic medications, anabolic agents, and drugs that block catabolism.[34]

**Prognosis**

The Glasgow Prognostic Index (GPI) uses serum C reactive protein and albumin in a three-stage system. The GPI independently predicted survival in potentially resectable pancreatic cancer in one study.[35] In a second study, the median survival of patients with a neutrophil/lymphocyte ratio (NLR) > 5 was 5.8 months, whereas patients with a NLR ≤ 5 who received palliative chemotherapy had a median survival of 10 months.[36] Evidence of inflammation in pancreatic cancer, therefore, is a poor independent prognostic factor regardless of stage.

**Quality of Life**

FDA approval of palliative chemotherapy is largely based on disease-free and overall survival, quality of life, and symptom reduction; the latter should be routinely measured by the treating oncologist. Physician assessments of symptoms underreport symptom severity compared to patient-reported symptom assessments. In patients with pancreatic cancer, quality of life improves with adjuvant chemotherapy (usually gemcitabine [Gemzar]), stabilizes along with stabilization of the cancer in response to first-line therapy, but significantly deteriorates with third-line chemotherapy.[37] Therefore, patients should not be treated with third-line chemotherapy unless in a research study, since this affords no survival, symptom, or quality of life benefit.
End-of-Life Care

Clinicians often do not recognize the signs and symptoms of dying, chief among which are cognitive dysfunction, anorexia, reduced fluid intake, Cheyne-Stokes respirations, jaw breathing, reduced urinary output, and skin mottling.[38] Common symptoms of dying, including anxiety, terminal restlessness, nausea, vomiting, pain, and respiratory tract secretions, should be managed with an opioid, haloperidol (Haldol) or other neuroleptic, a benzodiazepine, and an antimuscarinic.[39] Nine factors determine quality of life at the end of life. Factors that have a positive impact are religious prayer, meditation, pastoral care, and a therapeutic patient-physician relationship. Factors that have a negative impact are a hospital death, patient worry at baseline, cancer care at an inpatient site, feeding-tube placement, and chemotherapy in the final weeks.[40] Hospital volume also plays a role in the quality of end-of-life care. Small- and medium-volume hospitals are less likely to administer opioids, which reduce quality of life, while medium-volume hospitals are more likely to use the ICU or life-sustaining treatments for dying patients, which result in reduced quality of end-of-life care and cause complicated bereavement in surviving relatives.[41]

Suffering is distress related to events that threaten the intactness of the person.[42,43] There are three modern myths about suffering: 1) it is the same as physical pain, 2) it can be accurately measured, and 3) the most important priority is to eliminate suffering.[44] Suffering is promulgated through uncontrolled symptoms, social isolation, loss of self image, and existential angst. These factors need to be addressed by physicians. Hope counters suffering by fostering a sense that life continues to serve a purpose or hold meaning enough for continued existence.[45] Reminiscing and meaning- and dignity-based therapies improve hope. Empathy is the major physician attribute that enhances quality end-of-life care and ameliorates suffering. Empathy is the cognitive attribute that facilitates understanding of patient experiences, concerns, and perspectives, combined with the capacity to communicate this understanding.[46] Empathy improves communication and patient satisfaction, and reduces medical errors and professional burnout. Physicians are the therapy they deliver. The empathetic physician is to the patient what Virgil was to Dante as he traversed his inferno.[47]

Financial Disclosure: The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

References:


Source URL:

Links: