How I Treat . . .

How I Treat Pancreatic Ductal Adenocarcinoma

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The management of patients with pancreatic ductal adenocarcinoma is challenging. Patients tend to present with advanced disease and are more frail than age-matched counterparts with malignancies at other disease sites. Because of the location of the pancreas and the juxtaposition with stomach, small bowel, and common bile duct, these patients require multimodality management for decisions about surgical treatment or other interventions to address anatomic issues such as biliary obstruction or gastric outlet obstruction created by advancing disease.

This malignancy invades and metastasizes rapidly and early in its course. Thus, for patients who present with apparent localized and resectable disease, every effort should be made to understand the extent of disease and the likelihood of benefit with surgical treatment. All decisions about surgical treatment should be made in a multidisciplinary setting with the benefit of a computed tomography scan done with a "pancreas protocol" (ie, contrast administration and computed tomography settings to optimize visualization of the pancreas and surrounding organs) to be confident there is no direct tumor extension to the celiac axis or associated vasculature. Because the recurrence rate after surgery is high, even with additional adjuvant therapy, there is an increasing tendency to deliver neoadjuvant treatment with the hope of increasing the R0 (ie, complete resection without extension of the carcinoma to the surgical resection margins) resection rate. In addition, this buys time to judge the pace of disease in a given individual. If a patient experiences progression rapidly during the time they are receiving chemotherapy, they are obviously not candidates for definitive resection. The counter argument is that ineffective chemotherapy permits progression of disease.

At our institution, we currently favor resection followed by adjuvant chemotherapy with or without radiation. The impact of postoperative radiation in addition to systemic chemotherapy is uncertain, although one could certainly argue that this would be an important maneuver in the presence of margin-positive disease. Current data supports the use of chemotherapy alone either as a fluorinated pyrimidine or with gemcitabine.[1,2] Radiation, when administered, is usually given with continuous-infusion fluorouracil[3] or with oral capecitabine. Because of the many questions surrounding the appropriate adjuvant therapy for patients with resected disease, we favor clinical trial participation in this setting whenever possible.

Patients with locally advanced disease have a high risk of dissemination and one can assume that micrometastases exist even if not radiographically evident. For this reason, systemic chemotherapy is the first choice of therapy for this patient population. Both prospective and retrospective data suggest that radiation provides some additional benefit for those patients who are stable or experiencing disease regression after a few cycles of chemotherapy.[4,5]

Grossly metastatic disease requires systemic therapy. We believe that fixed dosage rate gemcitabine provides some additional benefit over standard infusion gemcitabine.[6,7] Because fixed dose rate as originally designed on the 3 week on/1 week off schedule is myelosuppressive, we have adopted an alternate-week schedule that seems to maintain efficacy based on two successive clinical trials.[4,8] To date, three drug combinations have shown some improvement in clinical outcome, such as time to progression or overall survival. These combinations include gemcitabine plus erlotinib,[9] cisplatin,[10] and capecitabine.[11] For patients not eligible for, or not treated on a clinical trial, we use fixed dose rate in combination with low-dose cisplatin because we have ample phase II data to support the safety and efficacy of this combination, although it has never been tested in a phase III trial. If one were to opt for gemcitabine and erlotinib or gemcitabine and capecitabine, it might be better to use the short infusion schedule of gemcitabine because that was the schedule tested in the randomized clinical trials showing additional benefit with erlotinib or capecitabine. Another potentially useful regimen, either in the first- or second-line setting is fluorouracil, folinic acid and oxaliplatin, or capecitabine and oxaliplatin. There is a bit more data available with the former.[12] This regimen has been compared with best supportive care in the second-line setting and was shown to improve survival.

Because patients with unresectable pancreatic cancer are usually frail and symptomatic from their disease, they often tolerate treatment poorly. In fact, it is often difficult even for the most experienced practitioner to discern treatment-related toxicity from disease-related toxicities, especially in the early phase of treatment. We have found that serial levels of CA 19-9 can be helpful when making early decisions about whether or not to continue treatment. Baseline CA 19-9 levels below 75 U/mL are probably not reliable for follow-up, and CA 19-9 is artifactually elevated in the setting of biliary ductal obstruction. For high CA 19-9 levels, a decrease of

10% to 20% in the first couple of months is extremely encouraging, and over time, a decrease of greater than 50% predicts well for prolonged survival and benefit from therapy.[14] In our experience, CA 19-9 measurements are as good as or perhaps better than radiographic findings, which can sometimes be misleading.

The palliative care needs of this patient population must be emphasized. Most patients present with common duct obstruction. Unless the patient is proceeding immediately to surgery, a stent should be placed. The choice of a plastic or metal stent depends on whether the patient is resectable and on the patient's projected life span. In general, expandable metal stents are preferred over plastic stents in patients who are not proceeding to surgery because these stents are less likely to occlude in the future and are associated with a much lower risk of cholangitis.

Pain is a predominant symptom for these patients. It tends to be located in the back as a result of encroachment of the celiac plexus. Many patients will benefit from a celiac block and it is our feeling that a block directed by endoscopic ultrasound is superior to other approaches. The combination of long-acting narcotics for round-the-clock pain control and short-acting narcotics for breakthrough pain is essential. Many patients experience situational depression and thus, consideration should be given to antidepressant therapy.

Because pancreatic ductal adenocarcinomas usually cause some degree of pancreatic ductal obstruction, pancreatic insufficiency is a frequent finding. This often is mild and can be confused with other symptoms of the disease. It is probably useful to give all patients a trial of pancreatic enzyme replacement to see if this will improve weight loss or postprandial symptoms of bloating, gas, nausea, and diarrhea.

Because of the location of the pancreas, duodenal and gastric outlet obstruction occasionally occurs. Unless the patient is extremely debilitated, surgical treatment is preferred. Duodenal stents can also be used if necessary.

Weight loss is a cardinal symptom in this disease. Although this may be due in part to pancreatic insufficiency, many patients also have cachexia from proteolysis and lipolysis. This is a difficult symptom to treat, although occasionally high-dose progesterone or fish oil can be useful in improving appetite and reversing weight loss.

Because there has been little impact on the overall survival of patients with pancreatic adenocarcinoma during the last few decades, a continued emphasis on clinical trials for all aspects of care and management is important. In addition, it has become increasingly evident that we must find opportunities to develop biorepositories of clinically annotated tissue that can be explored for new therapeutic targets or for biomarkers for early detection.

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