New Directions in Systemic Therapy of Pancreatic Cancer

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Background: The aggressiveness of pancreatic adenocarcinoma makes it a deadly disease, with its incidence rate and fatality rate almost equal. Surgery represents the only means to provide cure to patients with pancreatic cancer; though the 5-year survival is less than 10%.

Methods: We review the data on surgical and systemic therapies and provide more details on a newer biologically based medical approach.

Results: Neoadjuvant chemotherapy protocols are confined to one or two institutions, and adjuvant chemotherapy and chemoradiation therapy protocols are far from being standardized. Chemoradiation therapy for locally advanced pancreatic cancer offers limited benefits. Protocols that include gemcitabine and 5-fluorouracil, while comparing favorably to historical controls, offer median survivals at approximately 8 months.

Conclusions: More effective protocols with combinations of approaches agents are needed to improve the treatment of pancreatic cancer.

Introduction

Pancreatic cancer is an aggressive cancer. The incidence of pancreatic cancer is increasing, but little progress has been made in long-term survival. It remains one of the few cancers whose death rate nearly equals its incidence. As we enter the new century, the 2-year survival rate associated with pancreatic cancer remains approximately 10%.

There are many reasons why survival with pancreatic cancer is poor: (1) The symptoms and signs of pancreatic cancer are so nonspecific that patients often present with the disease in an advanced stage. Patients who present with jaundice generally have a better prognosis than patients who do not have jaundice because this condition causes patients to seek care when their cancers are at an earlier stage. (2)
Because symptoms and signs are nonspecific, physicians may not make the diagnosis of pancreatic cancer and thus may allow the tumors to further advance. (3) Increasingly, bureaucratic delays in our health care system prolong time from diagnosis to definitive care, potentially impacting survival. Patient delay, physician delay, and system delay result in patients presenting with advanced disease and promote the need for improved therapy for patients with advanced stage pancreatic cancer.

Though many modalities are available to diagnose or stage pancreatic cancer, computed tomography (CT) scan remains the relative gold standard. Unresectability by CT scanning is accurate to 95%, but resectability by CT scan is accurate to only 70%. Patients thought to have unresectable tumors will generally undergo further testing to document unresectability of their cancers. These additional tests may include angiography with venous phase study or CT portography. Recently, the role of magnetic resonance imaging (MRI)-cholangiography has been emphasized in the diagnosis and preoperative staging of pancreatic cancer. We have not been so impressed with MRI studies because fine details generally are not apparent. Laparoscopy, even though adding expenses to the cost of care, has an increasing role in intraoperative staging of pancreatic cancers, mainly by detecting small peritoneal implants and small superficial liver metastasis.

Percutaneous fine-needle aspiration or biopsies of pancreatic cancers should be undertaken only in selected patients because of risks of dissemination. Also, sampling error will occur and will serve to understage cancers or will fail to document existing cancers. Fine-needle aspiration and percutaneous biopsy have a role only in patients with unresectable disease when the intent is to document the unresectable nature of the pancreatic cancer. For example, a liver biopsy establishes not only the cancer, but also its advanced stage and unresectable state. Patients with pancreatic masses that appear resectable at CT should not undergo percutaneous biopsy or fine-needle aspiration. Such procedures violate the tumors and, whatever the outcome, will not change the therapeutic plan, though they may disseminate cancer cells.

The specific cause of pancreatic cancer remains unknown. Rather, it seems most likely that there are many causes of pancreatic cancer. The genetic alterations in patients with pancreatic cancer are notable and are increasingly well described. Marked abnormal karyotypes are found in 40% of patients with pancreatic cancer. Fractional arm loss on chromosomes correlates with prognosis and may involve chromosomes 1, 6, 7, 9, 12, 13, 17, 18, and 20. Alterations in a host of genetic markers such as k-ras, raf, DCC, and p53 have been well described. Mutations at these sites impart a poorer prognosis.

Resection offers the only hope of cure in treating pancreatic cancer. That concept is often lost in the therapeutic plan. Resection should be aggressively sought and pursued. Unfortunately, operability is relatively low and resectability is lower yet. This results in only a minority of patients with pancreatic cancer undergoing resection with curative intent. Resection without curative intent offers improved survival when compared to unresectable tumors. Operative mortality over the years has decreased, but survival with resection remains less than 20% at 5 years in most studies. These numbers not only underscore the need for systemic therapy for patients who are inoperable, but also emphasize the need for improved adjuvant therapy for patients who undergo surgery for cure.

Postoperative staging can be helpful in estimating survival. Several factors have been found to correlate with survival: tumor size, nodal status, distant metastasis, genetic markers (eg, p53, k-ras, etc), lymphatic invasion, perineural invasion, and surgical margins. Of these many factors that are important in postoperative staging, surgeons have control over only the surgical margins. Clean surgical margins should be aggressively sought; however, the size of the tumor, presence of lymph node metastases, and perineural invasion may preclude long-term survival even with clean surgical margins. This illustrates the futility of aggressively seeking clean surgical margins in patients with advanced primary tumors.

Neoadjuvant Therapy in Pancreatic Cancer

Neoadjuvant therapy has been advocated by some to improve curative resection rates and survival. Proponents hypothesize that neoadjuvant therapy decreases the chance of leaving microscopic and gross residual disease at the time of resection and thus decreases the chance of intraoperative peritoneal tumor spread. Neoadjuvant regimens would allow delivery of radiation to well-oxygenated cancer cells and would avoid delays of chemotherapy due to complications after resection. On the other hand, neoadjuvant therapy can delay surgical treatment of pancreatic cancer, and it carries its own morbidity.

Neoadjuvant therapy trials have been reported by many, including investigators at the University of Texas M.D. Anderson Cancer Center and Fox Chase Cancer Center. Most studies involved limited numbers of
patients, and most reported on combinations of 5-fluorouracil (5-FU) or cisplatin with external-beam radiation therapy (EBRT).\textsuperscript{8,9} Patients undergoing neoadjuvant chemoradiation therapy at M.D. Anderson Cancer Center experienced a lower rate of local recurrences, but 25% of those studied were unable to receive postoperative adjuvant treatment because of prolonged recovery after resection. Unfortunately, regimens have varied from study to study, and many trials involved historical controls. Due to the variability among the studies, the study designs and sizes, and the therapies chosen, neoadjuvant chemotherapy has not been conclusively shown to improve survival for patients undergoing resection for pancreatic cancer.

**Adjuvant Therapy in Pancreatic Cancer**

There are no established guidelines for adjuvant therapy following pancreatectomy. Several chemotherapy trials have been undertaken over the years. Many of these trials have included radiation therapy. These trials have produced varied results with varied regimens, often involving historical controls. Because of the limited scientific design of these studies and the lack of particularly efficacious therapy, the role of chemotherapy and radiation therapy remains generally unestablished.

Patterns of failure after pancreatectomy are notable, for they tell where the adjuvant therapy should be directed. Following pancreatectomy, recurrent disease generally appears within the nodal basin first. Approximately 80% of all failures will occur locoregionally. Sites of locoregional recurrence generally are the lymphatic tissues and nodes along the superior mesenteric vein, the portal vein, and the superior mesenteric artery.

Given sufficient time, recurrent disease will appear in many different organs and locations. Distant failure following pancreatic resection usually occurs in the liver and by spread through the peritoneal cavity. Hepatic metastasis may be seen in as many as 60% of patients in large series, and peritoneal metastasis may occur in as many as 40% of patients following pancreatectomy. The appearance of cancer in distant organs and at multiple sites generally follows locoregional recurrence and presages rapid deterioration and death.

Several chemoradiation studies in patients with resectable pancreatic cancer have been undertaken. However, these studies generally were not well designed, either involving small numbers of patients or undertaking comparisons with historical controls. Consequently, these trials failed to establish therapy guidelines in the treatment of pancreatic exocrine adenocarcinomas. The two most widely noted studies of adjuvant treatment of pancreatic cancer are the Gastrointestinal Tumor Study Group (GITSTG) trials\textsuperscript{10,11} published in 1985 and 1987. The 1985 trial was a prospective, randomized study of patients with pancreatic cancers undergoing pancreatectomy. This trial randomly assigned therapies between a control arm (only resection, 22 patients) and a treatment arm (resection followed by 5-FU and EBRT, 21 patients). The trial showed a survival benefit between the treated group (median survival = 21 months) and the control group (median survival = 11 months) (P=0.3). Subsequently, the second trial of the GITSTG reported a median survival of 18 months in 30 patients undergoing EBRT and 5-FU therapy after pancreatic resection. The small number of patients enrolled from multiple centers over an extended period of time, the absence of a control arm in the second paper, and the inclusion of patients with cancers of the pancreatic head, body, and tail raised questions about the reliability of the data. Though these trials have been widely quoted, their shortcomings are major liabilities. Conclusions from these studies should not be accepted without considerable reservations.

Preliminary results of a phase III trial from Europe,\textsuperscript{12} reported in abstract form, that compared EBRT plus 5-FU with follow-up chemotherapy (folinic acid followed by 5-FU) to no adjuvant treatment failed to demonstrate survival advantages in treated patients following pancreatic resection. Median survival was 23.5 months for patients receiving adjuvant therapy compared with 19 months for patients undergoing surgery only. This is the largest trial of adjuvant therapy for pancreatic cancer and has accrued more than 400 patients to date.

Few studies have investigated the role of chemotherapy as sole adjuvant treatment after pancreatic resection. A randomized study from Europe,\textsuperscript{13} published in 1993, accrued nearly 60 patients over a 4-year period. Patients were randomized to either a control group (pancreaticoduodenectomy only) or a treatment group (surgery plus polychemotherapy). The polychemotherapy regimen included 5-FU, doxorubicin, and mitomycin C. This trial documented a substantial advantage in median survival in the treated group (23 months vs 11 months), but treated patients experienced considerable toxicity that often required hospitalization. In addition, adjuvant polychemotherapy proved not to be beneficial at longer follow-up (the 5-year survival rate in the treated group was 8% vs 4% in the control group). The number of patients entered over a significant time span raises concerns about any differences in survival that might be suggested.

Intraoperative postresection radiotherapy (IORT) has been applied as adjuvant treatment of pancreatic cancer.
cancer. No controlled, randomized study has compared survival and outcomes among patients undergoing IORT, EBRT, or control therapy. Apparently, IORT results in fewer local recurrences but higher perioperative complication rates.\textsuperscript{14} No role for IORT has been established, though IORT has been widely applied, mostly in the 1980s.

Adjuvant intra-arterial regional chemotherapy has been studied in a few trials involving small numbers of patients. Link et al\textsuperscript{15} reported adjuvant intra-arterial polychemotherapy on 20 patients and documented median survivals of 21 months. The rationale behind this treatment is to deliver high doses of drug to the resected tumor bed. Potential drawbacks are arterial complications (eg, thrombosis), dislodgment of the catheter, mucosal damage from the injection of the chemotherapeutic agent, and dispersion of the drug due to the rich vascular arterial network of the celiac trunk and the superior mesenteric artery.

No studies document definitive efficacy of adjuvant therapy. The two studies from the GITSTG and, more recently, the larger European trial referred to above have demonstrated some advantage of adjuvant treatment for patients with pancreatic cancer. Generally, trials of adjuvant treatment of pancreatic adenocarcinoma included small numbers of patients or were poorly controlled. Though there are reports purporting efficacy of adjuvant therapy, the scientific validity of the reports is generally lacking. Therefore, the applicability and implications of the results of these trials need to be cautiously interpreted. Unfortunately, there remains no well-accepted, effective “gold standard” for treating patients in an adjuvant setting with pancreatic cancer.

Given the inefficacy of adjuvant therapy, we believe that surgeons who aggressively resect pancreatic cancers have an obligation to seek new and innovative ways to promote not only survival in patients following resection, but also survival and quality of life in patients who have unresectable disease.

Therapy for Locally Advanced Pancreatic Cancer

For patients with unresectable pancreatic cancer or with residual cancer after resection, there are no established guidelines for therapy. Most frequently, drugs such as 5-FU, mitomycin C, and cisplatin are combined with some form of radiation therapy. Polychemotherapy has not shown any advantage over single-chemotherapy regimens. Better results with radiation therapy seem to occur with combined chemotherapy and radiation therapy.\textsuperscript{16} Many patients currently receive a combination of 5-FU and EBRT, though there is not a strong database to support this approach. Though studies are available to support this standard, studies of significant numbers and sound design are lacking.

More recently, gemcitabine, a deoxycytidine analogue capable of inhibiting DNA replication and repair, has been used in the treatment of advanced pancreatic carcinoma. Gemcitabine was compared to 5-FU in a prospective, randomized trial using “clinical benefit response” as a marker of efficacy.\textsuperscript{17} Clinical benefit response was measured by analgesic consumption, pain intensity, performance status, weight change and, as a secondary end-point, survival. In this trial, emphasis was placed on quality of life rather than on survival. Randomization involved 126 patients, with 63 patients receiving either gemcitabine or 5-FU. The patients receiving either therapy were of similar age, and a similar number had stage IV disease. Clinical benefit response favored patients receiving gemcitabine, though the number of patients involved was small. Of patients receiving gemcitabine, 14 (22%) experienced a clinical benefit response, whereas of patients receiving 5-FU, only 3 (5%) experienced a clinical benefit response. Though these numbers seem different, it is noted that the number of patients in the study is small. Survival with gemcitabine was longer on average than with 5-FU (5.7 months and 4.2 months, respectively). The probability of surviving 1 year for those receiving gemcitabine was 18% compared with 2% for those receiving 5-FU. These survival numbers are neither significantly different nor impressive. They point out the aggressive nature of pancreatic cancer and the resistance of these cancers to systemic chemotherapy.

Since many studies utilized historical controls when evaluating therapy for pancreatic cancer, conclusions from such studies can be accepted only with trepidation and uncertainty. Nonetheless, when considering new therapies for patients with unresectable pancreatic cancer, it is important to remember that survival with 5-FU is only 2% at 1 year and mean survival is 4.2 months. Similarly, it is important to remember that gemcitabine alone is associated with an 18% probability of 1-year survival and a mean survival of 5.7 months. These poor survival statistics have led us to seek other avenues of therapy.

Several phase I and II trials, which included combinations of EBRT, 5-FU, and gemcitabine, coupled with other drugs such as epirubicin or cisplatin, have been reported recently. Most of these reports demonstrated that the combination of 5-FU and gemcitabine is safe and well tolerated in most patients with advanced pancreatic cancer. These results, though better than those with historical controls, are not promising, with median survival at best around 10 months.\textsuperscript{18,20}
The survival of patients presenting with local recurrence after “curative” pancreatic resection for malignancy is dismal at best. Standardized therapeutic options are lacking. Surgery with resection of recurrent tumor masses represents a formidable undertaking, is generally not possible, and is not considered conventional, but sometimes it can offer advantages in survival. Effective chemotherapy and radiation therapy protocols for inoperable recurrent disease are lacking. Recently, intra-arterial polychemotherapy has been proposed to palliate recurrent disease after pancreatic resection. Initial results appeared to be satisfactory, particularly in terms of pain relief, but long-term survival remains poor.

Metalloproteinase Inhibition in the Treatment of Pancreatic Cancer

The breakdown of extracellular matrix and the disruption of cellular architecture are the hallmarks of cancer. Metalloproteinases degrade all components of extracellular matrix, including fibrillar and nonfibrillar collagens and basement membrane glucoproteins. In this way, metalloproteinases promote the breakdown of extracellular matrix and the disruption of intercellular architecture, allowing for aggressive contiguous growth and systemic dissemination of cancers. In addition, metalloproteinases promote angiogenesis.

Metalloproteinases are present in high levels in a host of solid organ cancers. We and other investigators have found matrix metalloproteinase (MMP) gene expression to be increased in pancreatic cancers relative to normal pancreas. MMP gene expression is increased for multiple forms of MMPs including MMP-2 and MMP-9. MMP-2 seems particularly important in the growth and dissemination of pancreatic cancer.

We studied 21 human pancreatic cancers for MMP content and found that tumor levels of MMP-2 in the active form strongly correlate with nodal status and tumor stage. To a lesser extent, MMP-9 in the active form correlates with nodal status and stage. Neither MMP-9 nor MMP-2 in the active and latent form correlates with tumor size, implying that tumors with low MMP levels can grow to a large size prior to dissemination.

To study the role of metalloproteinase inhibition in the growth and dissemination of human pancreatic cancer, we used a nude mouse model of human pancreatic cancer. In this effort, cancers resected from patients have been grown in cell culture. Cancer cells were then operatively implanted into the head of the pancreata of the mice. Survival studies were undertaken, and serial evaluations of tumor growth were conducted. Necropsies allowed us to study cancer implantation and tumor growth.

It seems clear that, in this model, metalloproteinase inhibition by the metalloproteinase inhibitor Batimastat (BB-94) impeded implantation, delayed tumor growth, and prolonged survival. In study after study, mice begun on Batimastat as long as 1 week following operative implantation of neoplastic cells had a lesser rate of tumor implantation than mice receiving vehicle control. In general terms, implantation decreased by 15% in mice receiving BB-94 even when therapy was started as long as 1 week following tumor cell implantation. The specific cause of this is not known, though it seems that the efficacy of the metalloproteinase inhibitor is such that the immune status of the mouse is sufficient to eliminate all traces of the injected cancer cells.

Mice receiving the parenteral inhibitor Batimastat have been shown in a host of ways to have smaller tumors. Tumor weight and tumor volume were reduced by the inhibitor and, consistent with this, CA 19-9 levels were dramatically reduced in mice that were given Batimastat. Metalloproteinase inhibition was also associated with less tumor invasion and fewer metastases in this mouse model. Survival in mice that were given Batimastat was significant and surpassed survival in mice given the vehicle control, further promoting the efficacy of metalloproteinase inhibition.

We found improvements in survival in study after study, even when therapy is initiated at a time distance from implantation. Survival particularly improved when therapy was initiated prior to tumor implantation. Survival of mice starting Batimastat therapy prior to tumor implantation was almost indefinite and was indistinguishable from mice receiving sham injections rather than injections of cancer cells.

Combining Cytotoxic Therapy With Metalloproteinase Inhibition

Gemcitabine and metalloproteinase inhibitors obviously have different mechanisms of action. The possibility of having added efficacy with combination therapy must be considered and the possibility of synergistic activity may be possible. However, given their differences in action, different and varied complications may be possible with such therapy and as well, and accentuated or exaggerated complications may occur. To investigate the possibility of added efficacy with combination therapy, we studied the combination of gemcitabine and Batimastat in the nude mouse.
model of human pancreatic cancer utilizing a well-established, well-differentiated human pancreatic adenocarcinoma cell line (HPAC).²⁷

As seen in our previous studies, cancer cell implantation in mice receiving vehicle control was not uniform. Approximately 10% of mice receiving vehicle control beginning 1 week following cancer cell implantation did not harbor malignancy at necropsy. Similar but slightly diminished rates of implantation were seen in mice receiving Batimastat or gemcitabine. Mice receiving Batimastat and gemcitabine had greatly diminished rates of implantation, as the vast majority of mice receiving such therapy did not experience successful implantation of cancer cells, even though therapy was started 1 week following operative orthotopic implantation of cancer.²⁷ While this impedes the study of cancer growth in mice receiving this combination therapy, it documents that combination therapy offers new hope of controlling pancreatic cancer, particularly in circumstances of minimal cancer. This suggests a role for such combination therapy for patients in need of adjuvant therapy.

Studying only mice that had cancer, after eliminating all mice that did not demonstrate implantation of cancer at necropsy, survival was significantly promoted by combination therapy of Batimastat and gemcitabine.²⁷ With combination therapy, mice with cancer experienced indefinite survival, which ended only with sacrifice. Similar to our other studies, mice receiving vehicle control had progressive decreases in survival beginning at 40 days following implantation. This survival curve was relatively poorer, though not statistically different than survival curves associated with Batimastat or gemcitabine alone. Other previous studies of ours have shown significant differences in survival between mice receiving vehicle control or Batimastat, but this specific trial to test combination therapy did not. Similar to these differences in survival, assessment of tumor MMP levels shows that mice receiving gemcitabine in combination with Batimastat had lower levels of active and latent MMP-2 and MMP-9 compared with vehicle control. Lowest levels of active and latent MMP-2 and MMP-9 were seen with combination therapy relative to other forms of therapy and particularly relative to vehicle control. Similarly, serum MMP levels were lowest in mice receiving combination therapy.²⁷

Metalloproteinase Inhibition in Patients With Pancreatic Cancer

There is a growing body of data documenting the efficacy of metalloproteinase inhibition for patients with cancer. Patients diagnosed with small-cell lung cancer, melanoma, ovarian cancer, and pancreatic cancer have been studied. A survival study²⁸ involving patients in the United States and the United Kingdom with inoperable pancreatic cancer was undertaken in the early 1990s. This trial was designed to mirror in many ways the inclusion criteria utilized when 5-FU was compared to gemcitabine in patients with inoperable pancreatic cancer. CA 19-9 levels were used as a surrogate marker of efficacy in this trial, as the mechanism of MMP inhibition seems to be optimally studied through such a surrogate marker. Patient criteria included unresectable pancreatic cancer and an increasing CA 19-9 of 25% or more in the month prior to inclusion into the trial. Given this patient population, 74 patients were studied and only 3 patients were later excluded. Median survival was 125 days upon conclusion of the trial, with a number of patients still alive. Survival to 365 days was estimated to be approximately 30%. With all the caveats of using historical controls, this number seems superior to the 18% 1-year survival commonly associated with gemcitabine.

Patients could be divided into two groups based on the rate of rise of CA 19-9 following initiation of therapy. Retrospectively, it was observed that patients who continued to have a rise in their CA 19-9 of more than 25% in the month following initiation of therapy had a poorer outcome, with a projected survival of approximately 22% at 1 year. Patients with a decrease in the rate of rise in their CA 19-9 or had an actual decrease in their CA 19-9 following initiation of therapy had a much better survival rate, which approached 60% at one year.²⁸,²⁹ This gives hope that patients early in the course of their therapy could be evaluated for response and therapy could be continued for patients with a high probability of long-term survival.

Gemcitabine has been compared to an oral metalloproteinase inhibitor, Marimastat (BB-2156), in a prospective, randomized clinical trial³⁰ that was presented at the American Society of Clinical Oncology meeting in 1999. This randomized trial compared Marimastat to gemcitabine as first-line therapy for patients with unresectable pancreatic cancer. The randomized comparison involved three dose levels of Marimastat vs a standard regimen of intravenous gemcitabine. A total of 414 patients were enrolled to receive either Marimastat (5 mg, 10 mg, or 25 mg b.i.d.) or gemcitabine (1,000 mg/m²). The objective of this trial was to evaluate survival (as a primary end-point) and time to disease progression (as a secondary end-point). Additionally, quality of life, safety, and tolerability were secondary end-points.

All patients entering into the trial had histological or cytological diagnosis of unresectable pancreatic...

Primary mortality analysis documented that patients receiving 5 mg or 10 mg of Marimastat b.i.d. had similar survival curves. These curves were significantly inferior to patients receiving gemcitabine or the 25 mg b.i.d. dose of Marimastat. Survival with the 25 mg b.i.d. dose of Marimastat was similar to that achieved with gemcitabine.

The median time for disease progression was 56, 59, and 57 days for Marimastat doses of 5 mg, 10 mg, and 25 mg b.i.d., respectively. Median time to disease progression by gemcitabine was significantly longer (115 days) (P<0.001). Patients with liver metastases seemed to survive longer with gemcitabine, while patients with extensive locoregional disease seemed to survive longer with Marimastat therapy.

Studies of safety and tolerability documented few adverse effects in patients receiving either gemcitabine or Marimastat. Patients receiving any of the four therapies had similar numbers of adverse events. Most of the adverse events were mild, and many of them were more consistent with the underlying cancer than the therapy being tested, such as vomiting, nausea, and constipation. Of significant complications, gemcitabine was more often associated with hematologic complications such as leukopenia and thrombocytopenia. The metalloproteinases inhibitors were more often associated with musculoskeletal complaints, the majority of which were self-limiting. Musculoskeletal complaints with metalloproteinase inhibition involved the hand (particularly the dominant hand), followed by the shoulder, then the lower extremeties. Most of the musculoskeletal complaints were minor, but they were the primary reason for dose reduction and drug holiday for patients receiving Marimastat.

This randomized study comparing Marimastat to gemcitabine as a first-line therapy in patients with unresectable pancreatic cancer documents no significant difference between the survival curves associated with 25 mg b.i.d. of Marimastat or with gemcitabine. In that regard, this study did not meet its end-point. One-year survival associated with 25 mg b.i.d. of Marimastat was the same as that for patients receiving gemcitabine. The Cox proportional hazards model documented a dose-dependent effect of Marimastat, with patients receiving 25 mg b.i.d. surviving longer than patients receiving lesser doses. Although there were differences in tolerability, gemcitabine and Marimastat were generally well tolerated with no marked differences in safety. Expected hematologic complications (gemcitabine) and musculoskeletal complications (Marimastat) were seen. Complications associated with rapid disease progression were noted, but they did not affect the trial outcomes.

A multicenter study comparing gemcitabine with gemcitabine plus Marimastat is currently in progress at our institute. Data from this trial should be available in the near future.

Conclusions

No effective therapy guidelines have been established for patients with pancreatic cancer, whether measurable or microscopic disease. Though neoadjuvant and adjuvant therapy have support, studies undertaken to document efficacy have too often been flawed in design and have involved therapies that are generally inefficacious. Therapy for measurable residual or unresectable pancreatic cancer is attractive in concept, though scientifically proven effective regimens have yet to be established to provide for extended survival. More effective therapies are being sought. Until the results of studies of these approaches are available, patients with pancreatic cancer would best be served by participation in clinical studies that involve that offer real hope of progress rather than new ways to use 5-FU.

References

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