UPDATE IN CANCER CHEMOTHERAPY: GASTROINTESTINAL CANCER, CANCER OF THE PANCREAS

Jane C. Wright, MD
Bronx, New York

An update of the state of the art of cancer chemotherapeutic treatment of gastrointestinal tract cancer is described in this multiple-part series. A review of cancers of the colon, rectum, and anus was published in the April and May issues of the *Journal*. In this section, cancer of the pancreas and its treatment with surgery, radiation therapy, chemotherapy, and adjuvant chemotherapy are discussed.

Cancer of the pancreas has been on the increase in incidence in the United States during the past two decades. This increase in reported cases is second only to that of lung cancer. Pancreatic cancer now ranks fifth as a cause of cancer deaths, exceeded only by cancer of the lung, large bowel, breast, and prostate. In 1984 it was estimated that 23,000 people in the United States would develop cancer of the pancreas and that most of these would die of the disease. This dismal prognosis is due to late detection of the disease and to the relative ineffectiveness of available therapy.

The etiology of cancer of the pancreas is unknown, but it is believed to be associated with environmental factors such as chemicals (eg, nitrosoureas), radiation, and smoking. A recent study implicated coffee consumption as a factor, but this awaits confirmation.[164]

The majority of pancreatic carcinomas are adenocarcinomas, which occur more frequently in men than in women. Over the age of 40 years, the incidence increases with advancing age.

Because of the vague nature of the symptoms (except for jaundice), the location of the pancreas, the low diagnostic accuracy of the traditional radiographic examinations (especially the upper gastrointestinal series), detection of cancer of the pancreas at an early and more curable stage has been difficult. Only since the availability of computerized tomography (CT) scanning and sonography has it become possible to diagnose cancer of the pancreas more precisely, especially those lesions over 2 to 3 cm in diameter. While ultrasound is useful in distinguishing cysts and pseudocysts from neoplasms, it does not provide the detailed view of the pancreas, biliary tract, abdominal lymph nodes, and liver as the CT scan does. Hence, CT scanning is considered the state of art, the most useful method for evaluating the pancreas. In addition, these techniques also serve to monitor fine needle aspirations of pancreatic masses. Second-line procedures of diagnostic use are invasive and include percutaneous transheptic cholangiography (PTC), endoscopic retrograde cholangiopancreatography (ERCP), and selective arteriography. With superselective angiography, lesions under 2 cm in diameter can be visualized. Circulating tumor markers such as carcinoembryonic antigen (CEA) and α-fetoglobulin and pancreatic oncofetal antigen (POA), while not specific, may also aid in diagnosis. As some of the newer diagnostic tools (eg, nuclear magnetic resonance) are more fully evaluated, it is hoped that it will be possible to detect pancreatic cancer at even earlier stages.

Requests for reprints should be addressed to Dr. Jane C. Wright, New York Medical College, Department of Surgery, 234 East 149th Street, Bronx, NY 10451.

The only hope of cure for carcinoma of the pancreas is surgery. Surgery, however, is generally restricted to tumors in the head of the pancreas, since those in the body and tail are rarely diagnosed early enough to permit resection. Only 10 to 25 percent of patients with carcinoma of the head of the pancreas are resectable. The general surgical procedure employed is either the Whipple procedure (pancreatoduodenectomy-resection of the pancreatic head, duodenum, and stomach with three anastomosis and bilateral vagotomy) or a total pancreatectomy (removal of entire pancreas with the distal stomach and duodenum). While cure rates in some series, which include occasional cases of islet cell or ampillary carcinoma, range from 15 to 20 percent, a five-year survival rate of under 10 percent is probably more representative.[165] The operative morbidity and mortality from both procedures is high and, depending on the skill of the surgeon, ranges from 7.5 to 23 percent.[166-168]

Surgical palliation even in patients not possibly surgically curable is important. Gastrointestinal and biliary tract bypass procedures provide enormous relief from the discomfort of bile retention and duodenal obstruction and offer some prolongation of survival in a small percentage of patients (up to a few years) as compared with those given no palliative procedures.[165,169] Crile[169] noted that patients with symptomatic carcinoma of the head of the pancreas who underwent bypass procedures and biopsy survive longer than those with radical pancreatectomy.

The median survival time for patients with carcinoma of the pancreas is usually four months, and untreated patients are generally dead within one year. In a Mayo Clinic series of 145 cases with histologically proven incurable cancer of the pancreas, the median survival rate was 3.5 months, with a range of four weeks to 10 years.[27]

RADIATION THERAPY

Radiation therapy is only of palliative value in the treatment of advanced pancreatic carcinoma. Conventional dosages of 3,000 to 4,000 rad have provided equivocal results. In two uncontrolled studies, larger doses of radiation up to 6,000 rad and over have been reported to provide some increase in the survival rate.[170,171] These results have compared favorably with the benefits of radical "curative" surgery in the series of 31 patients from Massachusetts General Hospital where the incidence of local regional failure was 50 percent.[172] In a review of 3,610 patients with cancer of the pancreas, there were only 33 patients alive at five years, which clearly indicates the need for other approaches to the treatment of this disease.[171]

The combination of radiation and fluorouracil (FU) has become popular in the treatment of advanced cancer of the pancreas. In the randomized Mayo Clinic study, the combination of FU therapy followed by radiation resulted in five months of extra survival (mean survival 10.4 months).[173] Subsequently, the Gastrointestinal Tumor Study Group randomized 194 patients into three arms: (1) 4,000 rad plus FU; (2) 6,000 rad plus FU; and (3) 6,000 rad alone.[174] There were no significant differences in the two combination groups. The 86 patients in the high-dose radiation plus FU group had a mean survival rate of 11.5 months, and the 83 patients in the lower dose radiation plus FU group had a mean survival of 8.5 months. Of the 25 patients in the high-dose radiation group alone, the mean survival rate was 5.3 months. There were roughly 40 percent of the combined therapy patients alive at one year compared with only 10 percent of the radiation therapy group. More toxicity was noted in the high-dose radiation arms. As a result of this study, even though most of the patients in the combined therapy arm died within two years, the current recommendation for the treatment of locally unresectable pancreatic carcinoma is radiation of 6,000 rad total dose over six to 10 weeks with cycles of FU 500 mg/m^2/d intravenously (IV) the first three days of each 1,000-rad split course, followed by two weeks of rest, then repeated cycles. After the radiation is completed, maintenance therapy with FU is suggested.

Investigations underway in pancreatic cancer include interstitial implantation of high energy radionuclides and intraoperative radiation.

CHEMOTHERAPY OF CANCER OF THE PANCREAS

The chemotherapy of cancer of the exocrine pancreas is at best palliative. Tumor regressions and relief of symptoms have been achieved with chemotherapy, yet true complete remissions and long-term disease-free survival rates have not yet been achieved. However, some signs of progress with the use of chemotherapy are beginning to emerge.

The development of chemotherapy in the treatment of cancer of the pancreas has been slow. While most of the drugs in widespread use have been explored in pancreatic cancer, there is a paucity of data in large series of cases. Evaluation of response to chemotherapy is particularly difficult because of the location of the pancreas and the difficulties of definition in serial CT scans, ultrasonography, and liver scans where only lesions over 3 cm in diameter are acceptable as measurable. Therefore, not all cases of advanced disease have measurable lesions. In addition, the usual strict criterion of a clear 50 percent or more reduction in the size of the tumor as a response is even more difficult to establish. Evidence of symptomatic clinical improvement, such as decrease in pain, improvement in appetite, and feeling of well-being, has been reported by some as a response. In patients placed on chemotherapy immediately following bypass procedures, which in themselves can provide clinical improvement such as disappearance of jaundice and weight gain, it is difficult to distinguish how much of the improvement is due to the chemotherapy and how much is due to the surgery alone. Many reports do not stratify this subset of cases in addition to the other postoperative changes in the evaluation of the results of chemotherapy.

Single cancer chemotherapeutic agents with activity in adenocarcinoma of the pancreas are the same as those effective in other adenocarcinomas of the gastrointestinal tract. The main difference is some small variation in the percentage of reported response rates. Fluorouracil, the first and most widely employed active agent in carcinoma of the pancreas, has a reported range of response from 0 to 67 percent. Patient selection, response criteria, dosages, and scheduling account in large part for these variations. In collected series there was a response rate of 28 percent for fluorouracil, but more recent studies report a rate of only 20 percent.[175] In collected series the response rates for the two other drugs widely studied in pancreatic cancer are 27 percent for mitomycin C and 30 percent for the nitrosourea streptozocin. The Gastrointestinal Tumor Study Group reported a response rate of 13 percent (2/15) with single-agent doxorubicin (Adriamycin).[176] Recent reported single-agent response rates of drugs with activity are as follows: fluorouracil, 26 percent; mitomycin C, 27 percent; CCNU (lomustine), 16 percent, streptozocin, 11 percent; doxorubicin, 8 percent; and MeCCNU (semustine), 6 percent.[177-180] The remissions produced in pancreatic carcinoma with the use of single agents are partial, under 30 percent and usually only a few months in duration. It has been noted that patients who respond to therapy generally survive longer than do nonresponders.[30] Secondary responses after single-agent FU have been achieved in some cases with the administration of the alkylating agents, nitrosoureas, methotrexate, doxorubicin, mitomycin, and VP-16.[30]

Combination chemotherapy in pancreatic carcinomas has produced somewhat higher response rates than single-agent therapy. Objective response rates of up to 43 percent, with up to 5 percent complete remissions (but with fewer than 10 percent of responses lasting up to one year) have been reported.[181] However, many multiinstitutional studies in advanced pancreatic cancer have shown overall disappointing results with both single agents and combination therapy. Fluorouracil, which has been incorporated in almost all of the combination trials, has often been given in nonoptimal schedules.

Some two-agent combination trials have demonstrated moderate activity in pancreatic cancer. In studies with FU plus carmustine (BCNU) Kovach et al[182] achieved a 33 percent (10/30) objective response rate and Lokich and Sharin,[183] 27 percent (4/15). These regressions rarely extended over 4 to 8 months. A lower response rate of 10 to 15 percent was obtained in a trial by Stephens et al[184] with the combination of FU plus BCNU without spironolactone, but with

TABLE 7. SELECTED UNCONTROLLED TRIALS OF COMBINATION CHEMOTHERAPY IN ADVANCED PANCREATIC CANCER*

Regimen	No. of Patients Treated	Objective Response (%)	Median Survival (Weeks)	Study Group
Streptozocin, mitomycin C, fluorouracil (SMF)	23	43	24	Wiggans et al[197]
	22	32	24	Bukowski et al[188]
	28	14	19	Smith et al[198] (GITSG)**
SMF (loading)	27	15	13	Smith et al[198]
Fluorouracil doxorubicin, mitomycin (FAM)	15	40	15	Bitran et al[201]
	27	37	24	Smith et al[200]
	30	13	12	Smith et al[198]
Fluorouracil, doxorubicin, cisplatin (FAP)	21	24	16	Moertel et al[204]

*From O'Connell[181]
**Gastrointestinal Tumor Study Group

the addition of spironolactone, there was a slight but nonsignificant survival advantage. Combination trials of semustine (MeCCNU) plus FU have resulted in general low rates of response, namely 5, 10, and 17 percent.[185-187] In the phase III study of Buroker et al[187] where the combination of FU plus MeCCNU was compared with FU plus mitomycin C, objective regression occurred in 30 percent of patients in the mitomycin combination arm as compared with 17 percent in the other group. In the subsequent Southwest Oncology Group study of FU plus mitomycin, there was only a 5 percent response from the combination.[188] In an Eastern Cooperative Oncology Group (ECOG) study the combination of FU plus streptozocin vs streptozocin plus cyclophosphamide resulted in a 12 percent response in both arms with a survival rate in the range of five months.[189] Another two-agent study resulting in a 30 percent response was with the use of FU plus doxorubicin in the North Central Cancer Treatment Group study.[190]

The most impressive results with combination therapy in pancreatic cancer was Waddell's 1973[191] report of a 77 percent (10/13) response rate in patients treated with a combination of 5-FU plus testolactone or testolactone and spironolactone. In this study there was a historic control group treated with FU plus warfarin (Coumadin). The median survival rate of the patients treated with FU plus the lactone was over 31 months. This result was not confirmed by the phase III ECOG trial, which showed that lactones added nothing to the efficacy of therapy and that combination therapy with median survival rates were only 15 weeks.[192] Table 6 shows prospectively randomized clinical trials of chemotherapy in advanced pancreatic cancer.[181,193,194]

The current popular combinations of chemotherapy employed in the treatment of advanced adenocarcinoma of the exocrine pancreas include: streptozocin, mitomycin C, and 5-fluorouracil (SMF); 5-fluorouracil, doxorubicin (Adriamycin), and mitomycin C (FAM); fluorouracil, doxorubicin, and cisplatin (FAP); and fluorouracil, cyclosphosphamide, vincristine, and methotrexate (FCOM). It is with these combinations that the best results thus far have been achieved in pancreatic cancer, primarily in uncontrolled trials. Response rates up to 43 percent have been observed. However, median survival times range up to approximately six months, with the exception of the randomized trial of Mallinson et al[195] with the use of FCOM induction therapy followed by FU plus mitomycin maintenance therapy. Here median survival times of 11 months were obtained in the treated group as compared

TABLE 6. RANDOMIZED COMBINATION TRIALS IN ADVANCED PANCREATIC CANCER

Regimen	No. of Patients	Objective Response (%)	Median Survival (Weeks)	Study Group
Fluorouracil (FU), carmustine (BCNU)	30	33	24	Kovach et al[182]
FU	31	16	26	Kovach et al[182]
BCNU	21	0	22	Kovach et al[182]
FU*	89	—	18	Moertel et al[193]
FU, streptozocin*	87	—	16	Moertel et al[193]
FU, streptozocin	42	12	13	Moertel et al[189]
Streptozocin, cyclophosphamide	51	12	9	Eastern Cooperative Oncology Group[185]
FU, mitomycin C	45	22	19	Buroker et al[185]
FU, semustine (MeCCNU)	43	5	17	Buroker et al[185]
FU, MeCCNU	41	10	13	Horton et al[186]
FU, (MeCCNU), streptozocin	43	7	12	Horton et al[186]
FU, mitomycin C	50	5	15	Bukowski[188]
Streptozocin, mitomycin, fluorouracil (SMF)	45	40	16	Southwest Oncology Group[188]
Fluorouracil, doxorubicin, mitomycin (FAM)	56	9	28	Oster et al[194]
Streptozocin, mitomycin, fluorouracil (SMF)	66	4	18	Cancer and Acute Leukemia Group B[194]
FU**	11	36	23	Cullinan et al[190]
Fu, doxorubicin**	10	30	23	North Central Cancer Treatment Group (NCCTG)[190]
Fluorouracil, doxorubicin, mitomycin (FAM)**	13	8	17	NCCTC[190]
FU, methotrexate, vincristine, cyclophosphamide induction				
FU, mitomycin C maintenance	21	—	44	Mallinson et al[195]
Supportive care group	19	—	9	

*One half of patients also randomly assigned to receive spironolactone
**Survival rate comparisons based on patients with measurable and advanced nonmeasurable pancreatic cancer. Total number of patients treated: FU, 50; FU + doxorubicin, 45; FAM, 50

with nine months in the control group.[195] Table 7 indicates the results of selected uncontrolled trials of combination therapy in advanced pancreatic cancer.[181]

In 1977 Alberhalden and associates[196] at the Cleveland Clinic first demonstrated the effectiveness of the combination of streptozocin, mitomycin C, and 5-fluorouracil (SMF) in the treatment of 21 patients with pancreatic cancer. There were objective regressions of 50 percent or more in the size of tumors in 31 percent (5/16) of the evaluable patients and stable disease in 12 percent (2) for a total of 43 percent. Major toxicities with the combination included moderate leukopenia, thrombocytopenia, mucositis, and hypoglycemia. Subsequently, Wiggans et al[197] from Georgetown University confirmed the activity of the SMF combination in a carefully done phase II study in a series of 23 patients with good performance status where a response rate of 43 percent was obtained.[197] The median duration of response was in excess of seven months, and responders survived longer than nonresponders (7.5+ months vs 3 months). One patient with biopsy-proven liver metastasis

had a complete response and was alive and disease-free 3½ years following diagnosis. The SMF schedule employed was streptozocin 1 g/m² IV weeks 1, 2, 5, and 6, mitomycin 10 mg/m² IV week 1, fluorouracil 600 mg/m² weeks 1, 2, 5, and 6 with a repeat of the SMF cycle week 9. Downward adjustments were made in the dosages of fluorouracil and mitomycin according to the nadir of hematologic toxicity. Major side effects seen in the generally well-tolerated regimen included nausea and vomiting and nephropathy from the streptozocin. The high response rate in this single institutional study has been attributed to the careful adjustment of dosages, a good risk group of patients, the administration of earlier postoperative therapy, and the skill of the clinicians in the administration of chemotherapy. This serves to illustrate why phase II studies are usually more favorable than subsequent phase III studies of multi-institutional groups. The greater the number of institutions, the greater the likelihood of factors that will have an unfavorable impact on the response. The more recent Gastrointestinal Tumor Study Group study failed to confirm the high activity of SMF in pancreatic cancer.[198]

Because of nephrotoxicity in the SMF trials, streptozocin was dropped from the combination and doxorubicin was added to produce the combination of fluorouracil, doxorubicin (Adriamycin), mitomycin (FAM). In the initial trial of FAM, Smith et al[199] achieved a partial response rate of 40 percent (10/25) in patients with advanced cancer of the pancreas. Further studies of FAM in pancreatic cancer produced response rates of 37 and 40 percent.[200,201] Median survival time of responders was one year as compared with 3.5 months for nonresponders. The FAM regimen consisted of FU 600 mg/m² IV days 1, 8, 28, 36, and 56; doxorubicin 30 mg/m² IV days 1 and 28; and mitomycin 10 mg/m² days 1 and 56 with repetition of the cycle every 56 days. When streptozocin was added to FAM (FAM-S), Bukowski et al[202] obtained a response rate of 48 percent (12/25) in pancreatic cancer with a median duration of response of 4.5 months and a median survival rate of responders of 10.75 months as compared with two months for the nonresponders.[202] In general the FAM regimen has been tolerated better than the SMF regimen. Reports from the Gastrointestinal Tumor Study Group (GITSG), the Cancer and Acute Leukemia Group B, and the North Central Cancer Treatment Group have been unable to reproduce the high objective response rates with the FAM regimen.[190-194,198]

In the GITSG evaluation of SMF vs FAM vs streptozocin, doxorubicin, MeCCNU (SAME), the SMF combination was found to be the most active with an overall response rate of 43 percent.[16] In the recently published phase III the Southwest Oncology Group trial demonstrated objective regressions in 34 percent (19/56) patients following treatment with SMF.[203]

The combination of fluorouracil, doxorubicin, and cisplatin (FA) in the trial of Moertel et al[204] produced only a 24 percent response rate without prolongation of survival in patients with cancer of the pancreas.

The most interesting and well-tolerated regimen in the treatment of inoperable pancreatic carcinoma is that reported from England by Mallinson et al[195] consisting of induction chemotherapy with the combination of fluorouracil, methotrexate, vincristine, and cyclophosphamide followed by maintenance therapy with FU plus mitomycin. In this prospective randomized controlled trial of 40 patients, the median survival rate in the 21 treated patients was 44 weeks, which was significantly longer than the nine weeks in the 19 untreated controls. This prolongation of survival compares favorably with previous reports of chemotherapy with or without radiotherapy. The North Central Cancer Treatment Group is currently conducting a confirmatory trial of this regimen. In Greenspan's[30] small series of patients, a gratifying and surprising duration of secondary regressions was achieved with the use of fluorouracil, cyclophosphamide, and methotrexate (FCM). With the addition of vincristine to make FCOM, further encouraging results are being achieved. To this FCOM regimen alternating doses of doxorubicin and mitomycin are being added every three weeks.

Interest in adjuvant chemotherapy for pancreatic carcinoma has been slow to develop. Only one controlled randomized adjuvant trial has been conducted in patients with resected pancreatic

cancer treated with adjuvant combined radiation and 5-fluorouracil. In this GITSG study, 43 patients were randomized following subtotal pancreatic resection or total pancreatoduodenectomy to either receive no further therapy or to receive 4000 rad of split-course irradiation (2,000 rad courses) plus FU 500 mg/m^2 daily on the first of three days of each course of radiation therapy followed by weekly FU therapy for two years or to receive no further therapy after surgery.[205] The median survival rate was 20 months for the adjuvant treated group compared with 11 months for the control group ($P < .03$). There was an estimated two-year survival rate of 42 percent for the treated group vs 15 percent for the control group. Further trials of adjuvant therapy will be of interest and perhaps lead to an improvement in the cure rate of pancreatic cancer.

Progress in the chemotherapy of adenocarcinomas of the exocrine pancreas has been modest. Single-agent FU in advanced pancreatic cancer produces remission in approximately 20 percent of patients with median survival times of approximately six months and a 25 percent one-year survival rate. Combination chemotherapy with SMF and FAM have in some trials produced higher response rates than FU alone, but survival times have not been confirmed to be significantly increased. The combination of FCOM followed by maintenance FU and mitomycin has produced significant increased survivals in one trial, but awaits confirmation. With the development of new effective drugs and combinations of drugs with surgery and radiation therapy, there is reason to hope for better management in cancer of the pancreas.

CHEMOTHERAPY OF ENDOCRINE PANCREATIC TUMORS: ISLET CELL AND SECRETORY TUMORS

The endocrine tumors of the pancreas are rare. Approximately 190 new islet carcinomas are diagnosed each year in the United States. Islet cell tumors are both benign and malignant, and the establishment of malignancy is difficult since histology alone is unreliable. There are five known endocrine cell types in the pancreas, and endocrine syndromes associated with each cell type are different. The islet cells (composed of alpha, beta, and delta cells) have multiple potentials and produce a variety of hormones, such as glucagon, insulin, somatostatin, gastrin, vasoactive intestinal peptide (VIP), serotonin (5-HT), adrenocorticotropic (ACTH), melanocyte-stimulating hormone (MSH), and secretin. The most commonly functioning islet cell tumor is the beta cell insulinoma, of which 90 percent behave as benign adenomas and 10 percent show metastasis. Both the benign and malignant insulinomas produce hypoglycemia after a period of fasting, which is associated with a high level of insulin in the plasma.

The treatment of islet cell carcinoma is primarily surgical. Other management consists of antihormonal therapy to ameliorate symptoms secondary to the hormonal secretions of the tumor and cancer chemotherapy to produce regressions of the tumor. The most commonly employed antihormone agents are diazoxide for insulinomas and cimetidine for Zollinger-Ellison syndrome. Diazoxide produces hypoglycemia as well as hypotension. Corticosteroids, which have been widely used in the treatment of both benign and malignant insulinomas, are not recommended because of inevitable disturbing side effects. The most interesting of the hormone antagonists are the somatostatin analogues, which can suppress hormone production up to eight hours when given subcutaneously to patients with insulinomas, glucagonomas, and gastrinomas.[206]

The evaluation of the chemotherapy of islet cell tumors of the pancreas is difficult because of the variations in the biological and clinical characteristics of the various malignant lesions. Criteria of response have included objective tumor regression, amelioration of hormone-related syndromes, and biochemical measurements of decreases in circulating hormone levels.

Islet cell carcinomas are responsive to both streptozocin and fluorouracil. Overall response rates to each of these drugs ranged from 25 to 35 percent, and long-term regressions have been noted.[30] Most of the single-agent chemotherapy of

these tumors has centered around streptozocin, a drug noted to produce a permanent diabetic state in rodents, dogs, and monkeys with a single intravenous dose by the selective destruction of the pancreatic B cells. Because of its diabetogenic property, streptozocin has been employed in the treatment of malignant insulinomas. In the review at the National Cancer Institute of 52 cases of islet cell carcinoma treated with streptozocin, there were 41 with functional tumors. Of these 64 percent of patients had a biochemical response and 50 percent had tumor regressions.[207] In the 29 patients in whom measurable disease was present, there was objective tumor regression in 48 percent and complete remission in 17 percent following therapy with streptozocin. There was a measurable decrease in the levels of plasma insulin in 60 percent associated with improvement in the quality of life of these patients. Responding patients survived longer than nonresponding patients. Median survival time was 744 days in the treated group vs 298 in the nonresponding group. Five deaths from renal failure occurred in the series from the streptozocin.

Combination chemotherapy with FU plus streptozocin in an Eastern Cooperative Oncology Group (ECOG) study produced results better than with FU alone.[208] With the combination therapy there were responses of 63 percent (25/40) compared with 34 percent (14/41) treated with FU alone. The duration of remissions was longer with the combination (in excess of $1^1/_2$ years). There were complete responses in 33 percent following the combination FU and streptozocin treatment lasting for $2^1/_2$ years. Median survival rates were 26 months for the combination and 16 months for FU alone. In this trial all functional variants of the islet cell carcinoma (insulin, Zollinger-Ellison, glucagon or serotonin producing) as well as the nonfunctioning tumors were reported to respond to the combination therapy. In the treatment of the malignant Zollinger-Ellison tumors due to "gastrinomas," experience is anecdotal. Three cases have been reported where there has been objective tumor regression associated with decrease in the level of circulating gastrin.[206]

The current recommended chemotherapy for islet cell tumors is FU 400 mg/m² IV daily for five days plus streptozocin 500 mg/m² IV daily for five days with repeat cycles every six weeks and with downward adjustment of dosages according to toxicity.

A study is now underway in the ECOG for the treatment of islet cell carcinoma comparing FU plus streptozocin vs streptozocin plus doxorubicin vs chlorozotocin as a single agent.

In the chemotherapy of non-beta cell islet neoplasms, current interest is with the combination of fluorouracil, streptozocin, and doxorubicin.

Literature Cited

30. Greenspan EM, Ratner LH. Gastrointestinal chemotherapy. In: Greenspan EM (ed). Clinical Interpretation and Practice of Cancer Chemotherapy. New York: Raven Press, 1982, pp 195-241.

164. MacMahon B. Risk factors for cancer of the pancreas. Cancer 1982; 50:2676-2680.

165. Moertel CG. Exocrine pancreas. In: Holland JF, Frei E III, eds. Cancer Medicine. Philadelphia: Lea & Febiger, 1982, pp 1792-1804.

166. Coutsoftides T, MacDonald J, Shibata HR. Carcinoma of the pancreas and periampullary region: A 41-year experience. Ann Surg 1977; 186:730-733.

167. Sato T, Saitoh Y, Noto N, et al. Follow-up studies of radical pancreaticoduodenal cancer. Ann Surg 1977; 186:581-588.

168. Ihse I, Lilja P, Arnesjo B, et al. Total pancreatectomy for cancer. Ann Surg 1977; 186:675-680.

169. Crile G. The advantages of bypass operation over radical pancreatoduodenectomy in the treatment of pancreatic carcinoma. Surg Gynecol Obstet 1970; 130:1049-1053.

170. Haslam JB, Cavanaugh PJ, Stroup SL. Radiation therapy in the treatment of irresectable adenocarcinoma of the pancreas. Cancer 1973; 32:1341-1345.

171. Dobelbower RR Jr. The radiotherapy of pancreatic cancer. Semin Oncol 1979; 6:378-389.

172. Tepper J, Nardi G, Suit H. Carcinoma of the pancreas. Review of MGH experience. Indications for radiation therapy. Cancer 1976; 37:1519-1524.

173. Moertel CG, Childs DS, Reitmeier JR, et al. Combined 5-fluorouracil and supervoltage radiation therapy of locally unresectable gastrointestinal cancer. Lancet 1969; 2:865-867.

174. The Gastrointestinal Tumor Study Group. Therapy of locally unresectable pancreatic carcinoma: A randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + fluorouracil) and high dose radiation + 5-fluorouracil. Cancer 1981; 48:1705-1710.

175. Macdonald JS, Gunderson LL, Cohn I Jr. Cancer of the pancreas. In: DeVita VT, Hellman S, Rosenberg SA, eds. Cancer Principles and Practice of Oncology. Philadelphia: JB Lippincott, 1982, pp 563-589.

176. Schein PS, Lavin PT, Moertel CG. Randomized phase II clinical trial of adriamycin in advanced measurable pancreatic carcinoma. A Gastrointestinal Tumor Study Group Report. Cancer 1978; 42:19-22.

177. Carter SK. The integration of chemotherapy into combined modality approach for cancer treatment. VI. Pancreatic adenocarcinoma. Cancer Treat Rev 1975; 2:193-214.

178. Moertel CG. Chemotherapy of gastrointestinal cancer. Clin Gastroenterol 1976; 5:777-793.

179. Gastrointestinal Tumor Study Group. Randomized phase II clinical trial of adriamycin, methotrexate, and actinomycin D in advanced measurable pancreatic carcinoma. Cancer 1978; 42:19-22.

180. Moertel CG, Douglass HO, Hanley J, et al. Phase II study of methyl CCNU in the treatment of advanced pancreatic carcinoma. Cancer Treat Rep 1976; 60:1659–1661.

181. O'Connell MJ. Current status of chemotherapy for advanced pancreatic and gastric cancer. Review article. J Clin Oncol 1985; 3:1032-1038.

182. Kovach JS, Moertel CG, Schutt AJ, et al. A controlled study of combined 1,3-bis(2-chloroethyl)-1-nitrosourea and 5-fluorouracil therapy for advanced gastric and pancreatic cancer. Cancer 1974; 33:563-567.

183. Lokich JJ, Sharin AT. Combination therapy with 5-fluorouracil (5-FU; NSC 19893) and 1,3-bis(chloroethyl)-1-nitrosourea (BCNU; NSC-409962) for disseminated gastrointestinal carcinoma. Cancer Chemother Rep 1972; Chemother Rep 1972; 56:653-657.

184. Stephens RL, Hoogstraten B, Hass C, et al. Pancreatic cancer treated with carmustine, fluorouracil and spironotaclone; a randomized study. Arch Intern Med 1978; 138:115-117.

185. Buroker T, Kim PN, Groppe C, et al. 5-FU infusion with mitomycin C vs 5-FU infusion with methyl CCNU in the treatment of advanced upper gastrointestinal cancer. Cancer 1979; 44:1215-1221.

186. Horton J, Gelber R, Engstrom P. Trials of single agent and combination chemotherapy for advanced cancer of the pancreas. Cancer Treat Rep 1981; 65:65-68.

187. Buroker T, Kim PN, Heilbrum L, et al. 5-FU infusion with mitomycin C (MMC) vs 5-FU infusion with methyl-CCNU (ME) in the treatment of upper gastrointestinal cancer. A phase III study. Proc Am Soc Clin Oncol 1978; 19:310.

188. Bukowski RM. Randomized comparison of 5-FU and mitomycin C (MF) versus 5-FU, mitomycin C and streptozocin (SMF) in pancreatic adenocarcinoma: A Southwest Oncology Group Study. Proc Am Soc Clin Oncol 1981; 22:543.

189. Moertel CG, Douglass HO, Hanley J, et al. Treatment of advanced adenocarcinoma of the pancreas with combinations of streptozocin plus 5 fluorouracil and streptozocin plus cyclophosphamide. Cancer 1977; 40:605-608.

190. Cullinan SA, Moertel CG, Fleming TR, et al. A comparison of chemotherapy regimens in the treatment of advanced pancreatic and gastric cancer. JAMA 1985; 253:2061-2067.

191. Waddell WR. Chemotherapy for carcinoma of the pancreas. Surgery 1973; 74:420.

192. Moertel CG, Lavin PT. An evaluation of 5-FU, nitrosourea and lactone combinations in the therapy of upper gastrointestinal cancer. Proc Am Soc Clin Oncol 1977; 18:344.

193. Moertel CG, Engstrom P, Lavin PT, et al. Chemotherapy of gastric and pancreatic carcinoma. Surgery 1979; 85:509-513.

194. Oster MW, Theologides A, Cooper MR, et al. Fluorouracil (F) + adriamycin (A) + mitomycin (M) (FAM) versus fluorouracil (F) + streptozocin (S) + mitomycin (M) (SMF) in advanced pancreatic cancer. Proc Am Soc Clin Oncol 1982: 1:90.

195. Mallinson CN, Rake MO, Cocking JB, et al. Chemotherapy in pancreatic cancer: Results of a controlled prospective, randomized multicentre trial. Br Med J 1980; 281:1589-1591.

196. Aberhalden RT, Bukowski RM, Groppe CW, et al. Streptozocin (STZ) and 5-fluorouracil (5-FV) with and without mitomycin C (Mito) in the treatment of pancreatic adenocarcinoma. Proc Am Soc Clin Oncol 1977; 18:301.

197. Wiggans RG, Wooley PV, MacDonald JS, et al. Phase II trial of streptozocin, mitomycin C and 5-fluorouracil (SMF) in the treatment of advanced pancreatic cancer. Cancer 1978; 41:387-391.

198. Smith FP, Stablein DM, Schein PS. Phase II combination chemotherapy trials in advanced measurable pancreatic cancer. Proc Am Soc Clin Oncol 1984; 3:150.

199. Smith FP, Macdonald JS, Wooley PV, et al. Phase II evaluation of FAM, 5-fluorouracil (F), adriamycin (A) and mitomycin C (M) in advanced pancreatic cancer (PC). Proc Am Assoc Clin Oncol 1979; 20:415.

200. Smith FP, Hoth DF, Levin B, et al. 5-Fluorouracil, adriamycin and mitomycin C (FAM) chemotherapy for advanced adenocarcinoma of the pancreas. Cancer 1980; 46:2014-2018.

201. Bitran JD, Desser RK, Kozloff MF, et al. Treatment of metastatic pancreatic and gastric adenocarcinomas with 5-fluorouracil, adriamycin and mitomycin C (FAM). Cancer Treat Rep 1979; 63:2049-2051.

202. Bukowski RM, Schacter LP, Groppe CW, et al. Phase II trial of 5-fluorouracil, adriamycin, mitomycin C and streptozocin (FAM-S) in pancreatic carcinoma. Cancer 1982; 50:197-200.

203. Bukowski RM, Balcerzak SP, O'Bryan RM, et al. Randomized trial of 5-fluorouracil and mitomycin C with or without streptozocin for advanced pancreatic cancer. A Southwest Oncology Group study. Cancer 1983; 52:1577-1582.

204. Moertel C, Fleming T, O'Connell M, et al. A phase II trial of combined intensive course 5-FU, adriamycin and cisplatinum in advanced gastric and pancreatic carcinoma. Am Soc Clin Oncol 1984; 3:137.

205. Kalser M, Ellenberg S, Levin B, et al. For the Gastrointestinal Tumor Study Group (GITSG). Pancreatic cancer: Adjuvant combined radiation and chemotherapy following potentially curative resection. Proc Am Soc Clin Oncol 1983; 2:122.

206. Macdonald JS: The endocrine pancreas. In: DeVita VT, Hellman S, Rosenberg RC, eds. Cancer Principles and Practice of Oncology. Philadelphia: JB Lippincott, 1982, pp 1001-1019.

207. Broder LE, Carter SK. Results of therapy with streptozocin in 52 patients. Ann Intern Med 1973; 79:108-118.

208. Hanley JA, Johnson LA. Randomized comparison of streptozocin alone versus streptozocin plus 5-fluorouracil in the treatment of metastatic islet cell carcinoma. Proc Am Soc Clin Oncol 1980; 2:415.