Low Dose Octreotide and Tamoxifen in the Treatment of Adenocarcinoma of the Pancreas

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Background. **Data from experimental studies suggest that a combination of octreotide, the long acting somatostatin analogue, octreotide, and tamoxifen improves the survival of animals with pancreatic cancer.**

Methods. **Twelve patients with a tissue diagnosis of ductal adenocarcinoma of the pancreas were treated with 100 μg of octreotide three times per day and tamoxifen 10 mg twice daily. The survival of the octreotide-tamoxifen group was compared with a historic cohort of 68 untreated patients with pancreatic cancer, matched for age, sex, and TNM stage.**

Results. **The median survival times for the octreotide–tamoxifen-treated group compared with the historic cohort were 12 and 3, months respectively. Actuarial one-year survival rates for the octreotide–tamoxifen-treated group compared with the historic cohort were 59% and 16%, respectively.**

Conclusions. **In this study, patients with unresectable and resected ductal adenocarcinoma of the pancreas had an apparently increased survival when treated with a combination of octreotide and tamoxifen. A randomized controlled trial to examine this potential therapeutic benefit is now indicated. *Cancer* 1995;75:23–8.**

Key words: pancreatic cancer, octreotide, tamoxifen, survival, somatostatin.

The incidence of adenocarcinoma of the pancreas in North America has risen steadily over the past four decades and presently stands at approximately 26,000 new cases per year.[1] It is the second most common gastrointestinal malignancy and the fourth leading cause of death from malignant disease.[1] The hallmarks of the disease are diagnosis at an advanced stage and an extremely poor prognosis. A meta-analysis of 144 reported series including approximately 37,000 patients reported that the median survival time was 3 months.[2] According to these findings, 65% of patients with pancreatic cancer will die within 6 months from the time of diagnosis, and about 90% within 1 year. Surgical resection, if performed early enough, is presently the only effective form of curative therapy.[3]

Successful treatment of carcinoma of the breast has been achieved by endocrine manipulations. The presence of estrogen receptors on neoplastic breast tissue is correlated with response to ovarian ablation and/or antiestrogen treatment. A similar approach to the treatment of pancreatic cancer seems justified because of the presence of estrogen receptors in pancreatic carcinoma[4–7] and in normal pancreatic tissue.[8,9] In fact, the use of tamoxifen in 80 patients with ductal adenocarcinoma of the pancreas has been reported in a case-control study to increase the median survival time from 3 months to 7 months.[10,11] However, steroid hormones may not be the most important regulator of pancreatic cell proliferation. Other potential influences include the growth factor IGF-1 and the growth inhibitor somatostatin.

Somatostatin decreases growth of the normal rat pancreas,[12] and at least one somatostatin analogue, SMS 201-995, inhibits the growth of human pancreatic adenocarcinoma in nude mice.[13] The demonstration of somatostatin receptors in exocrine pancreatic adenocarcinomas[14] and the large body of evidence[15–21] demonstrating antiproliferative activity of somatostatin and

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somatostatin analogues on experimental pancreatic neoplasms in vitro and in vivo, justifies clinical studies concerning a potential therapeutic role of these substances in pancreatic cancer. There is experimental evidence that somatostatin analogues may act directly on neoplastic cells by up-regulating activity of phosphotyrosine phosphatases,[22,23] an activity that would be expected to reduce proliferation stimulated by growth factors that act via tyrosine kinase signal transduction pathways. In addition, somatostatin analogues may act indirectly to reduce proliferation of somatostatin receptor positive or negative tumors by reducing levels of mitogens such as IGF-1. However, the use of native somatostatin is limited because of its very short plasma half-life and the need for continuous infusion. The recent development of long acting somatostatin analogues, such as RC160 and octreotide, however, has made clinical trials possible.

Preliminary results of somatostatin analogue therapy in patients with tumors other than pancreatic, have been encouraging.[24–27] When used alone at low dose, however, the long-acting analogue octreotide was reported to be ineffective in patients with advanced pancreatic cancer.[28,29] It is of considerable interest, therefore, to note that a combination of both octreotide and tamoxifen is effective treatment for human pancreatic cancers growing in nude mice.[18]

To further define a possible beneficial role for combination hormonal therapy with octreotide and tamoxifen, we studied the effect of chronic administration of these two inhibitory agents on survival of a prospective series of patients with resectable or unresectable adenocarcinoma of the pancreas.

Patients and Methods

Between 1990 and 1993, 12 consecutive patients with biopsy-proven ductal adenocarcinoma of the pancreas were referred for consideration of treatment to the Centre for Pancreatic Diseases at the Montreal General Hospital. Two of the patients had their diagnosis established by ultrasonically guided needle biopsy. A tissue diagnosis was established at laparotomy in the remaining 10 patients, including five at the time of double or triple bypass procedures, and 5 at the time of a Whipple's resection.

On confirmation of tissue diagnosis with proven residual or unresectable tumor, and after informed consent was obtained, self-administered treatment was begun with 100 μg of octreotide acetate (Sandostatin, Sandoz, Montreal, Canada) subcutaneously three times daily and 10 mg of tamoxifen (Rhone-Poulenc, Montreal, Canada) orally twice daily. Patients had regular follow-up examinations at 4- to 6-week intervals until the time of death. The major outcome was the median duration of patient survival in months from the time of diagnosis.

Table 1. Patient Characteristics

Characteristic	Octreotide/tamoxifen (n = 12)	Historic cohort (n = 68)
Age (± SD)	66 ± 11	66 + 4
Sex (M:F)	1:0.3	1:0.7
% Stage III or greater	67	66
No. resected (%)	5 (42)	9 (13)

SD: standard deviation.

Between 1985 and 1990, 99 consecutive patients with a biopsy-documented diagnosis of ductal adenocarcinoma of the pancreas were admitted to the Montreal General Hospital. Data was collected on age, sex, stage at diagnosis (based on the TNM Classification of the International Union Against Cancer), type of treatment and duration of survival from the time of diagnosis. Thirty-one patients were excluded because of the inability to determine the exact time of death.

The survival of the 12 patients treated with octreotide/tamoxifen was compared with that of a historic cohort of 68 patients. The clinical characteristics of both groups are shown in Table 1. The patient characteristics for the group of excluded patients did not differ from the cases or the controls with respect to age, sex, or stage of disease at diagnosis.

Descriptive data are expressed as mean ± SD for continuous, and proportions for categoric variables. Actuarial survival was calculated from the date of diagnosis by the Kaplan–Meier method. Where pertinent, the log-rank test was used to test the difference between the different survival curves and the Wilcoxon sign-rank test was used to test the difference between median survival times. Cox's proportional hazards model was used to evaluate between group differences with respect to survival from time of diagnosis, and examines the effect of treatment while controlling for the effects of resection. Three patients still alive in the octreotide/tamoxifen group at 8 (n = 1) and 12 (n = 2) months were treated as censored values where appropriate in the analysis. These patients remain well at the time of submission of this manuscript.

Results

Survival times measured from the date of diagnosis for the 12 patients treated with octreotide/tamoxifen and the 68 patients in the historic cohort are shown in Figure 1. The median survival times of the octreotide/tamoxifen-treated group and the historic cohort were 12

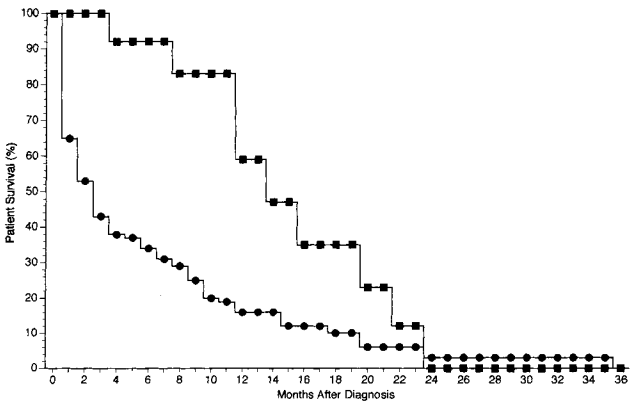

Figure 1. Actuarial survival for all octreotide/tamoxifen-treated patients (-■-, n = 12) and the historic cohort (-●-, n = 68).

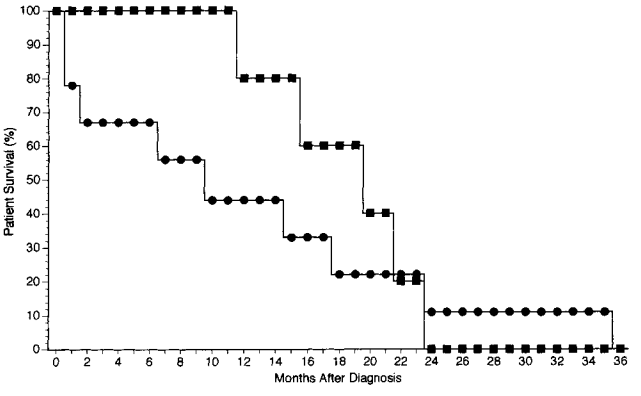

Figure 3. Actuarial survival for all octreotide/tamoxifen-treated patients (-■-, n = 5) and patients in the historic cohort (-●-, n = 9) that were resected.

months and 3 months, respectively, and the 1-year actuarial survival rates were 59% and 16%, respectively.

Figure 2 displays the survival curves of patients treated with octreotide/tamoxifen stratified according to whether they were resected (n = 5) or not resected (n = 7). The median survival times of the resected and the unresected patients were 20 months and 12 months respectively and the 1-year actuarial survival was 80% and 31%, respectively. Survival curves for the 5 resected octreotide/tamoxifen patients and the 9 resected patients in the historic cohort are shown in Figure 3. The median survival times of the octreotide/tamoxifen-treated group and the historic cohort were 20 months and 12 months, respectively, and the 1-year actuarial survival rates were 80% and 44%, respectively.

Figure 4 displays the survival curves for the 7 unresected patients treated with octreotide/tamoxifen and the 59 unresected patients in the historic cohort. The median survival times of the octreotide/tamoxifen-treated group and the historic cohort were 12 months and 2.5 months, respectively, and the 1-year actuarial survival rates were 31% and 11%, respectively.

In the historic cohort, patient survival did not vary significantly by sex. Among the treated patients, the median survival periods of the female (n = 4) and male patients (n = 8) were 13 months and 12 months respectively. These differences are understated because two of the three patients who remain alive are women.

Cox's proportional hazards analysis confirmed that treatment and resection both independently predicted a longer survival ($P < 0.01$). The significance of a possible interaction between both could not be fully determined because of the small sample size.

Although an assessment of quality of life and pain control was not prospectively assessed in this study, a post hoc analysis demonstrated that morphine sulphate was not required until the final 4–6 weeks of illness in 9 of 12 patients that had already succumbed to their disease. Of the three surviving patients, one takes 650 mg of tylenol with 30 mg of codeine on a per need basis and the other two do not require any analgesic medication.

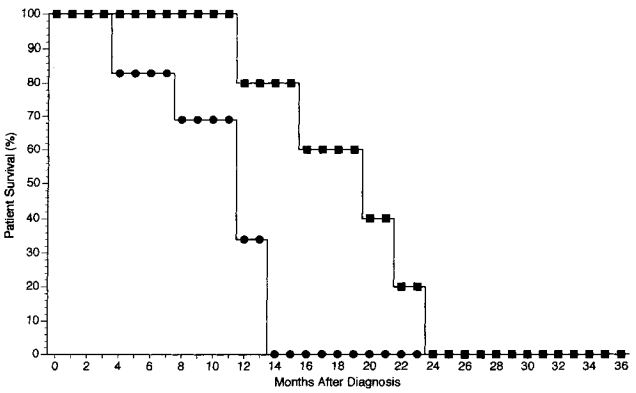

Figure 2. Actuarial survival of octreotide-tamoxifen-treated patients stratified according to whether they were resected (-■-, n = 5) or not resected (-●-, n = 7); $P < 0.05$ at one year.

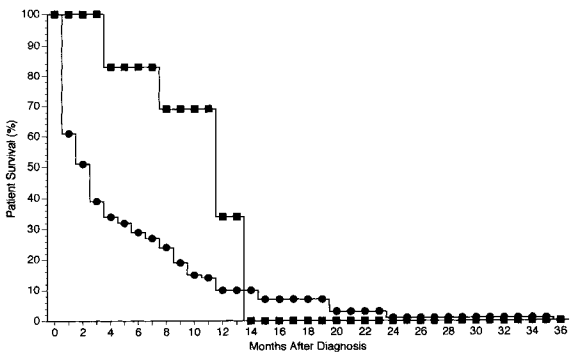

Figure 4. Actuarial survival for all octreotide/tamoxifen-treated patients (-■-, n = 7) and patients in the historic cohort (-●-, n = 59) that were not resected.

Computed tomography scanning examinations of the 12 patients were performed at intervals of 6 to 8 weeks. No objective responses were seen in terms of tumor regression; rather the data is more consistent with a slowing of tumor progression. The three surviving patients have stable disease.

The only identifiable side effect of the octreotide/tamoxifen therapy was mild to moderate steatorrhea in 7 of the 12 patients. This side effect resolved with dietary supplementation using exogenous pancreatic enzymes.

Discussion

Despite improvements in diagnostic imaging, ductal adenocarcinoma of the pancreas remains a disease that is diagnosed too late for effective treatment. The only hope is surgical excision, but fewer than 15% of patients are resectable.[28] Other more effective therapies, therefore, need to be developed.

Successful treatment of carcinoma of the breast by endocrine manipulation suggests that a similar approach to the treatment of pancreatic cancer is justified because of the presence of hormone receptors in pancreatic carcinoma.[5–7] Whereas the use of tamoxifen in patients with adenocarcinoma of pancreas has been reported to be of limited benefit in prolonging median survival,[11] the results achieved to date using long acting analogues of somatostatin in clinical studies, as opposed to animal or in vitro studies, have been disappointing.[28,29]

One possible explanation of the different results of animal and human studies with different analogues of somatostatin may be that there are different binding affinities of the various somatostatin analogues to somatostatin receptors.[14,30,31] Using one such analogue, octreotide, Reubi and colleagues[31] failed to identify somatostatin receptors in 12 samples of histologically proven human pancreatic cancer. This raises the question as to precisely how somatostatin analogues, and octreotide in particular, exert their antitumor effects. Recent progress in the field of somatostatin signal transduction has resulted in the cloning of five distinct somatostatin-binding cell surface receptors.[32] Ongoing work is underway to determine which of these mediates growth inhibiting effects, and to determine to what extent different somatostatin analogues, such as octreotide and RC-160, interact with each receptor subtype.[33]

A number of gastrointestinal hormones, including gastrin and cholecystokinin, have trophic effects on pancreatic tissue[34] and can stimulate the growth of pancreatic tumors. Somatostatin suppresses the secretion and action of these peptides, and this may contribute to its antiproliferative activity.[35,36] Somatostatin may also exhibit an antitumor effect by inhibition of the secretion of growth factors, such as epidermal growth factor and insulin-like growth factor-1, that are thought to be important in neoplastic processes.[37–41] The latter possibility is of considerable interest because both tamoxifen[41] and octreotide[42] have been shown to lower circulating levels of IGF-1 and the combination has recently been reported to lower IGF-1 levels more substantially than either agent alone.[43] This raises the possibility of therapeutic synergy if the two agents were used together, a combination that has recently been shown to be effective treatment for human pancreatic cancers growing in nude mice.[18] It was because of these experimental considerations that we undertook the present study.

A median survival time of approximately 3 months is the usual expectation for this disease.[11] In our study, treatment with octreotide/tamoxifen increased the median survival duration both in the resected group (from 2 months to 20 months) and unresected group (from 2.5 months to 12 months). We found, therefore, the combination of octreotide/tamoxifen to be of benefit in prolonging patient survival. Bias may have been introduced, however, because of the method of patient selection and the use, at least in part, of retrospective data.

Although 31 of 99 patients from the historic cohort were excluded because of incomplete data, there is a priori no reason to believe that these patients were different in any way than the other controls. Moreover, they were similar with respect to all examined variables.

The two groups compared in this study were similar with respect to age, sex, and stage of disease at the time of diagnosis. The greatest benefit of octreotide/tamoxifen therapy was found to occur in the nonresected group. We cannot confidently conclude the extent of its effect in the resected group of patients because of their small number.

Possible explanations for the apparent benefit of octreotide/tamoxifen therapy include (1) diagnosis of the controls later in the course of the disease, (2) diagnosis of the cases earlier in the course of the disease, or (3) a change in the biologic aggressiveness of the disease as a consequence of treatment. The first two explanations are unlikely as the data indicate that the stage at which the disease was diagnosed in cases and the cohort was similar. Although it might appear that more patients in the octreotide/tamoxifen treated group underwent resection, and were therefore "more curable," as stated above, the TNM stage at the time of diagnosis was similar in the two groups. In addition, since 1990, we have broadened our selection criteria for Whipple resection and have removed age as an absolute disqualifier. The criteria for ascertainment of the diagnosis and for staging, however, have remained unchanged since 1985.

The small number of cases in this study did not permit a stratified analysis of age, sex, or stage. In the historic cohort, patient survival did not vary according to sex. However in the octreotide/tamoxifen-treated group, a survival advantage for women is suggested, which is all the more significant, because three of these four patients were in the group that was not resected, and they would otherwise be expected to have a much poorer prognosis. This finding is similar to that reported by Wong and Chan.[11]

The final observation that warrants comment is the apparent analgesic benefit that the patients derived from the administration of octreotide. This unexpected finding, which requires more formal assessment, was brought to our attention by our patients, and in fact, most patients did not require morphine until the final stages of their disease—an experience distinctly different from that usually seen in patients with pancreatic cancer. This possible beneficial effect of octreotide may be related to its recognized effects in the central nervous system, to a locally mediated decrease of pancreatic secretion in a partially obstructed pancreas, or to a reduction in the degree of local inflammation.[44,45] These considerations aside, the possible placebo effect of having daily subcutaneous injections over an extended time also cannot be ruled out at this time.

In summary, our experience with the combination of octreotide and tamoxifen in the treatment of adenocarcinoma of the pancreas suggests that this regimen may be associated with favorable alteration of the aggressive biologic behavior of this disease and minimal toxicity. Our data justify the undertaking of a larger prospective randomized controlled trial. Such a trial is necessary to formally demonstrate any effect of this treatment on the natural history of pancreatic cancer, and would also provide an opportunity to carry out companion basic science studies regarding mechanism.

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