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Leuprolide and Tamoxifen in the Treatment of Pancreatic Cancer. A Phase II Study

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THE PRESENCE of oestrogen receptors and oestrogen binding proteins in normal and neoplastic pancreas gave rise to the hope that agents such as tamoxifen may be of value in the treatment of this deadly disease [1, 2]. However, subsequent clinical studies yielded a disappointing lack of unequivocal benefits, which suggested in some instances a prolongation of survival [3], but no evidence was found of a true objective response [4]. In more recent years, additional *in vitro* and *in vivo* data have outlined the potential role of luteinising hormone releasing hormone (LHRH) agonists alone [5] or in addition to somatostatin analogues [6] in experimental pancreatic cancer. An anecdotal report of tumour response has been reported in humans [7]. In view of these data, we have conducted a phase II study with leuprolide and tamoxifen, a combination of hormonal agents widely investigated in breast cancer. From December 1991 to May 1992, 15 consecutive patients with histologically proven pancreatic adenocarcinoma and no prior chemotherapy or radiotherapy entered this study, and were treated with leuprolide depot 3.75 mg intramuscularly every 4 weeks and tamoxifen 20 mg twice a day, continuously until progression. Baseline study parameters included performance status (at least 2 or better in the ECOG score), full blood count, CA19-9 level, chest X-ray, abdominal computed tomography scan (at least one site of radiologically measurable disease was required) and all patients gave informed consent prior to starting treatment. Evaluation of response and toxicity took place every 2 months according to WHO criteria [8].

No objective response was seen; 5 patients had stabilisation of the disease for a median duration of 4 months (range 3–7) and all these had received previous surgical palliative procedures (bypass). 10 patients progressed; the median survival of the entire group was 5 months (range 2–11). No decrease in CA19-9 levels (expressed by 11 cases) was noted and no clear evidence of an improvement in subjective symptoms such as pain or fatigue, was recognised. Side-effects were minimal: only 2 patients (one male) complained of hot flushes, and one male reported a reduced sexual function.

Table 1. Characteristics of patients

Entered/evaluable	15/15
Male/female	9/6
Median age, years (range)	56(37–73)
Median performance status (ECOG) (range)	2(1–3)
Previous palliative surgery (bypass)	8/15
Metastatic disease sites	9/15
Liver	5/15
Nodes	8/15
Peritoneum	2/15
Lung	1/15
Bone	1/15
Pretreatment elevated CA 19-9 levels	11/15

This negative experience is in accordance with two recently published trials with goserelin alone [9] or in combination with hydrocortisone [10]. A possible explanation of these dismal results might lie in the dosage of the LHRH analogues utilised, which were probably too low for a direct inhibitory effect. Future trials should focus on more potent LHRH analogues, perhaps in combination with slow release depot preparations of somatostatin analogues [6].

In conclusion, although there is currently a substantial amount of data suggesting the possibility of hormonal manipulation of exocrine pancreatic cancer, there is still a grim lack of clinical evidence to support this hypothesis. Pancreatic cancer remains one of the most devastating gastointestinal malignancies.

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1. Greenway B, Iqbal MJ, Johnson PJ, Williams R. Oestrogen receptor proteins in malignant and fetal pancreas. *Br Med J* 1981, **283**, 751–753.
2. Andren-Sandberg A. Estrogens and pancreatic cancer: some recent aspects. *Scand J Gastroenterol* 1986, **21**, 129–133.
3. Wong A, Chan A, Arthur K. Tamoxifen therapy in unresectable adenocarcinoma of the pancreas. *Cancer Treat Rep* 1987, **71**, 749–751.
4. Keating JJ, Johnson AMG, Cochrane BG, *et al.* A prospective randomised controlled trial of tamoxifen and cyproterone acetate in pancreatic carcinoma. *Br J Cancer* 1989, **60**, 789–792.
5. Redding TW, Schally AV. Inhibition of growth of pancreatic carcinomas in animal models by analogs of hypotalamic hormones. *Proc Natl Acad Sci USA* 1984, **81**, 248–252.
6. Szende B, Srkalovic G, Schally AV, Lapis K, Groot K. Inhibitory effects of analogs of luteininzing hormone-releasing hormone and somatostatin on pancreatic cancers in hamsters. *Cancer* 1990, **65**, 2279–2290.
7. Gonzales-Barcena D, Rangel-Garcia NE, Perez-Sanchez PL, Gutierrez-Damperio C, Garcia-Carrasco F. Response to D-TRP-6-LHRH in advanced adenocarcinoma of pancreas. *Lancet* 1986, **ii**, 154.
8. WHO Handbook for Reporting Results of Cancer Treatment. WHO offset publication No. 48. Geneva, WHO, 1979.
9. Allegretti A, Lionetto R, Saccomanno S, *et al.* LH-RH analogue treatment in adenocarcinoma of the pancreas: a phase II study. *Oncology* 1993, **50**, 77–80.
10. Philip PA, Carmichael J, Tonkin K, *et al.* Hormonal treatment of pancreatic carcinoma: a phase II study of LHRH agonist goserelin plus hydrocortisone. *Br J Cancer* 1993, **67**, 379–382.