Hormonal Therapy of Pancreatic Carcinoma

Rationale and Perspectives

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Summary

Exocrine pancreas carcinoma is still diagnosed at a relatively late stage, so that only a few cases can be cured by surgery. Therefore, it is desirable that an effective medical therapy be found first to stall the development of the disease and second to improve the life conditions of patients. On the basis of recent discoveries, a new therapeutic approach seems to derive from hormone manipulation. The growth of pancreatic carcinoma appears to be stimulated by various factors, such as Epidermal Growth Factor (EGF) and Insulin-like Growth Factor I (IGF-I), and by various hormones, such as androgens and cholecystokinin. Several studies performed on cell lines and on animal models of pancreatic carcinoma demonstrated an antitumoral effect of certain antihormones and of somatostatin. Taking such studies as a premise, the first clinical studies were finally started in patients suffering from nonoperable pancreatic cancer. Results are still partial and contradictory, but such research is certainly worthy of further study along the lines already taken.

Key Words: Gastrointestinal hormones; growth factors; sex hormones; somatostatin.

Introduction

Pancreatic carcinoma has become a frequent disease and is now the fifth cause of death because of neoplasia in industrial countries (1,2). In the United States, it causes over 20,000 deaths per year (3), and in Italy the number of victims of the disease is at least 4000 each year (4).

In spite of considerable progress in image diagnostics (ultrasonography, CT, ERCP, and so on), the disease is generally diagnosed in its late stages (5), so that only about 15 to 20% of cases are surgically treated (6). Therefore, the prognosis of this illness remains poor: The mean survival time after diagnosis is about three months (7), and the survival rate after five years is less than 1% (8). Further, both chemio- and radiotherapy have proven to be unsuccessful both in modifying the progress of disease and in improving the patients' quality of life (9).

Recently, various experimental works have opened new perspectives into medical therapy of pancreatic carcinoma; they are especially concerned with hormonal manipulation, as had already been the case with prostatic and with mammary carcinomas. Such oncological research had principally two different aims: to improve the knowledge of biological features of neoplastic cells, especially in rela-
tion to the possible influence of hormones and growth factors on tumor proliferation, and to assess the presumed antitumoral effect of some hormones and antihormones in animal models of pancreatic carcinogenesis.

Experiments carried out on both animal models and neoplastic-cell cultures supplied evidence that tumor growth is actually affected by various humoral factors, both of the hormonal type and of the so-called growth factor type; some of these are produced not only by normal tissues of the body, but also by tumor cells (10,11). In fact, one of the trigger factors of abnormal tumor growth could precisely be an increased sensitivity to cell-proliferation stimulators (10,11). Such a phenomenon is common to other types of cancer.

Growth Factors

Epidermal Growth Factor (EGF) and its cellular receptor may play a very important role in the development of pancreatic carcinoma. EGF is a polypeptidic growth factor that is produced by various epithelial cells. EGF stimulates the proliferation of certain human pancreatic cancer cell lines (UCVA-1, T3M4, Capan-1, MiaPaCa-2, and so on.) (12,13). Such a stimulating effect is connected with the presence of specific EGF receptors in neoplastic cells (12-14). Overexpression of EGF receptors was detected in cells with structural alterations on the chromosome-7 short arm, that is to say the region that contains the EGF receptor gene (for this reason considered a proto-oncogene) (13). In the Capan-1 cell line two classes of EGF receptors were identified and their expression on the cellular membrane was found to increase or decrease by different treatments (15).

EGF receptors are made up of three domains: extra-cellular, trans-membraneous, and intra-cellular. EGF, binding itself to the extracellular domain of the receptor, activates it through autophosphorylation and starts a chain of intracellular enzymatic reactions, leading to cellular division or, at least, preparing it through centrosomal separation (16,17).

Some of the abovementioned cell lines were found to produce the Transforming Growth Factor-alpha (TGF-α) (18,19). This polypeptide, also produced by normal keratinocytes, shows a 35% homology of sequence with EGF and has 6 cysteine residues in the same positions as the corresponding EGF. Thus, the tri-dimensional configuration of these two factors is similar (20,21). Therefore, TGF-α seems to exert its biological action, at least partly, through its binding to the EGF receptor. Indeed, EGF effects are more or less intensely reproduced in several tissues by the TGF-α (20,21) and it has been shown that TGF-α is also capable of stimulating proliferation of certain human pancreatic carcinoma cell lines (up to 100 times more than EGF) (21).

Each such neoplastic cell lines might produce a growth factor, the TGF-α, which might in turn, through the EGF receptors, act on the cell itself and on the contiguous ones, thus supporting the abnormal tumor growth. This observation was the basis for the foundation of autocrine (and paracrine) activity of the neoplastic cell.

Another class of polypeptides, the Transforming Growth Factor-beta (TGF-β), produced by normal keratinocytes and by other cells, has an inhibitory effect on cellular proliferation in several tissues (20). Its role is important in controlling epithelial-mesenchymal interaction.

The above factors were found also in the periductular connective tissue of mouse normal pancreas. It was assumed that a reduced sensitivity of the neoplastic cells to these factors might contribute to the abnormal tumor growth (22).

Somatomedin Insulin-like Growth Factor-I (IGF-I) in the MiaPaCa-2 cellular line is another factor with autocrine activity. IGF-I is a polypeptide similar in structure to insulin and it has been shown to stimulate cell growth directly (18).

Sex Hormones

Pancreatic neoplastic cells are also affected by various sex hormones. Several epidemiologic and experimental data are now available regarding sex hormones. It may be noted that exocrine pancreas carcinoma is more frequent in the male than in the female, with a male/female ratio of about 2:1 (23). This ratio, however, is modified in most populations according to age: It is generally very high under 50 years of age, but decreases in persons over 70 years of age (23). These data indicate that the