

Foreword

Somatostatin plays an inhibitory role in the regulation of the function of a number of organs like the brain, the anterior pituitary gland, the gastrointestinal tract, the exocrine and endocrine pancreas, as well as lymphoid cells. It can be considered as an inhibitory (growth) factor in these organs, which mainly prevents local overreaction from a multitude of stimulatory factors.

In addition to the negative role in controlling the physiological regulation of these organ systems, somatostatin also exerts inhibitory effects on the proliferation of normal and neoplastic cells. Somatostatin analogs inhibit tumor growth in a wide variety of experimental models in several species, like transplantable osteo- and chondrosarcomas, transplantable acinar and ductal pancreatic carcinomas, as well as different types of rat and mouse mammary and prostatic carcinomas. Also, a number of human pancreatic, colonic, gastric and small cell lung cancer lines xenografted in nude mice are inhibited in their growth during therapy with somatostatin analogs.

While most of these experimental tumors and cell lines express a dense and homogeneous distribution of somatostatin receptors, some of these tumors seem to be inhibited in growth by somatostatin analog administra-

tion via indirect mechanisms involving inhibitory effects on local or general growth factors (growth hormone, insulin-like growth factor 1, epidermal growth factor, gastrointestinal hormones) and/or angiogenesis.

One should realize, however, that in most of the experimental models the inhibitory effects of somatostatin analogs on growth are most potent early after tumor implantation as well as early after the start of drug administration, and that complete growth curves of the (transplanted) tumors with and without somatostatin analog treatment often indicate a delay in growth only, while an escape of tumor growth from the inhibitory effects of somatostatin analogs is observed eventually. This indicates a decreased sensitivity of these tumors during long-term somatostatin analog therapy, which involves somatostatin receptor downregulation and/or the selection of somatostatin receptor-negative tumor cell clones.

In clinical oncology prostate, breast and endometrial carcinomas are known to be 'conditional' cancers, which grow in certain specific hormonal environmental conditions. When these conditions are altered the tumors regress, but do not die. After a certain period of a persistent nonproliferating state, part of

the tumor cells resume active growth. This is the simple basis for the success of androgen, estrogen and progesterone depletion in the treatment of these cancers. The symptomatic relief of patients with metastatic prostatic, breast and endometrial cancers during treatment with antiandrogens, antiestrogens and progesterone receptor-blocking agents is highly appreciated and looked for by oncologists that otherwise mainly use intensive chemotherapy.

The promising data demonstrating that many experimental tumor models also seem to be 'conditionally' dependent on somatostatin, growth hormone, insulin-like growth factor 1, prolactin and other hormones and growth factors has raised hopes that direct or indirect blockade of their activity and/or receptors on metastatic human cancers with well-tolerated drugs like somatostatin analogs, bromocriptine and retinoids would also induce a transient state of dormancy or even a slight temporary regression. Also, the somatostatin analog octreotide is widely and successfully used in patients with acromegaly, metastatic islet cell tumors and carcinoids. In these patients the quality of life improves and there is strong evidence for control of tumor growth as well as a clear prolongation of survival.

Like most hormone-secreting tumors many human adenocarcinomas originating from the breast, colon, kidney, ovary as well as meningiomas and malignant lymphomas often express somatostatin receptors. Although somatostatin receptors are in many cases not distributed homogeneously over all tumor cells, and their numbers per tumor cell in general are lower than in hormone secreting tumors, most somatostatin receptor-bearing human cancers can be visualized by somatostatin receptor imaging. Only little evidence so far indicates that long-term therapy of patients with somatostatin receptor-positive tu-

ors with somatostatin analogs induces a decrease or even control of tumor growth. More evidence points to a transient improvement in the quality of life in some of the patients treated.

Human cancers differ in many respects from the experimental tumor models that respond so well to somatostatin analog therapy. (1) Most human cancers consist of a mixture of varying amounts of stromal tissue and different clones of epithelial tumor cells that do not uniformly express somatostatin receptors. This sharply contrasts with the monoclonal tumor models in animals, which in most instances express somatostatin receptors on all tumor cells. (2) Somatostatin receptor expression in human breast, prostate and colonic cancers often indicates loss of differentiation of the tumors, meaning that these undifferentiated tumors have a bad prognosis. (3) The nature of new clinical trials in oncology is often such that patients are mainly included 'late' in their disease, when tumors have already progressed considerably. Also, it remains uncertain whether somatostatin receptor subtype 2 (SSTR-2)-specific analogs like octreotide are the optimal compounds to be used in the treatment of human cancer. These analogs have little activity towards the SSTR-3 subtype, which is important in mediating apoptosis. In vitro studies have demonstrated that SSTR-2-expressing tumor cell lines as well as primary cultures of human tumors internalize radiolabeled somatostatin analogs like ^{111}In -[DTPA⁰]octreotide and [^{90}Y -DOTA⁰, Tyr³]octreotide. Preclinical studies using experimental tumor models have now demonstrated that tumor growth can be inhibited by administration of these two radiopharmaceutical compounds. Clinical trials already demonstrated promising effects using these radiopharmaceuticals on tumor size in patients with advanced somatostatin receptor-positive neuroendocrine tumors. Also, the concept of

targeted chemotherapy to deliver chemotherapeutic compounds selectively to somatostatin receptor-positive tumor cells, thereby reducing their toxicity, has now been validated using newly developed cytotoxic somatostatin analogs in experimental mouse and rat models of human pancreatic, breast and prostate cancers.

In this supplement to *Chemotherapy* Professor Scarpignato has succeeded in bringing together the most knowledgeable scientists in the field of oncology that have extensive personal experience with the use of somatostatin analogs in the treatment of cancer patients.

They review the current status of their use in an admirable manner, while the perspectives of newer forms of therapy with the targeted somatostatin receptor-mediated approach are also discussed.

I would like to congratulate the editor and the contributors on the exhaustive and balanced description of the current thoughts on the use of somatostatin analogs in patients with different forms of metastasized cancer.

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