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Review

The role of somatostatin analogues in the treatment of neuroendocrine tumours

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Abstract

Neuroendocrine tumours belong to a heterogeneous family of neoplasms, originating in endocrine glands (such as the pituitary, parathyroid or the neuroendocrine adrenal glands), in endocrine islets (within the thyroid or pancreas) as well as in endocrine cells dispersed between exocrine cells throughout the digestive or respiratory tracts. The clinical behaviour of neuroendocrine tumours is variable; they may be functioning or not functioning, ranging from well-differentiated slow growing neuroendocrine tumours to poorly differentiated neuroendocrine tumours, which are highly aggressive malignant tumours. The development of somatostatin analogues as important diagnostic and treatment tools have revolutionised the clinical management of patients with neuroendocrine tumours. However, although symptomatic relief and stabilisation of tumour growth for various periods of time are observed in many patients treated with somatostatin analogues, tumour regression is rare. Development of new somatostatin analogues and new drug combination therapies should further improve the clinical management of these patients.

Keywords: Somatostatin; Octreotide; Neuroendocrine tumours

Contents

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1. Introduction

Neuroendocrine tumours (NETs) comprise a family of neoplasms that present with a fascinating range of morphologic, functional and behavioural characteristics (Oberg, 2005).

The traditional classification of NETs include tumours originating in the adrenal medulla and sympathetic ganglia, C cells of the thyroid gland, islets of the pancreas as well as in the endocrine cells distributed throughout the digestive or the respiratory tracts (Rindi et al., 2000; Solcia et al., 1999). NETs were first described in 1888 by Otto Lubarsch who found multiple ileal tumours in two patients at autopsy. It was then 15 years later that Oberndorfer introduced the term carcinoid for ileal tumours that presented a more benign disease course than that of colon carcinomas (Modlin et al., 2004). Subsequently, endocrine tumours of the gastrointestinal tract as well as lesions from other organs were called carcinoids, and were classified on the basis of the anatomic site of origin into *foregut carcinoids* (lung, thymus, stomach, pancreas, duodenum, upper jejunum), *midgut carcinoids* (lower jejunum, ileum, appendix, proximal colon) and *hindgut carcinoids* (transverse colon, sigmoid and rectum) (Caplin et al., 1998; Ganim and Norton, 2000b; Vinik et al., 1989). NETs originating from the gastrointestinal tract and the pancreas are also called gastroenteropancreatic neuroendocrine tumours (GEP NETs). According to the latest World Health Organization (WHO) classification (Solcia et al., 2000), which is based on tumour histology, tumour size and the presence or absence of local/distant metastases, NETs should be stratified into (a) well-differentiated neuroendocrine tumours, (b) well-differentiated endocrine carcinomas, (c) poorly differentiated neuroendocrine carcinomas and (d) mixed exocrine–endocrine carcinomas. The great majority of NETs are relatively slow growing (well-differentiated), while some of them may present with more aggressive behaviour (poorly differentiated neuroendocrine carcinoma); these latter are fast growing tumours and, therefore, highly malignant. The well-differentiated NETs have the important ability to take up neuroamines and to express specific receptors on their cell membrane, such as somatostatin receptors (SSTR), although not in all cases; this characteristic may be of great value for the localisation and the treatment of these tumours (Kaltsas et al., 2001). While a relatively wide variety of therapeutic options are available for treating these patients (e.g., surgery, somatostatin analogue therapy, interferon-α, peptide receptor radiotherapy, chemotherapy, chemo-embolisation, etc.), few are curative and most treatments are palliative. It is unclear as to why certain of these tumours remain localised and respond well to therapy, while others present with inoperable metastatic disease and severe hormonal symptoms (Eriksson and Oberg, 1999). Therefore, successful treatment of these diseases necessitates a multidisciplinary approach in order to control symptoms, to stabilise or prevent further growth and, rarely, to achieve cure.

The response of the tumour to different therapeutic options may be defined, according to established WHO criteria, as: (1) complete response (complete regression of all clinical, radiological and hormonal evidence of tumour); (2) partial response (a 50% or greater reduction in all measurable tumour, clinical symptoms and hormonal levels, with no appearance of new lesions); (3) stable disease (less than 50% reduction or no greater than 25% increase in tumour size, clinical symptoms and hormonal measurements) and (4) progression (appearance of new lesions, or an increase of 25% or more in tumour size, and clinical/hormonal deterioration) (Arnold et al., 2000).

In this review we will summarise the literature regarding the role of somatostatin analogues in the diagnosis and mostly in the treatment of gastroenteropancreatic (GEP) NETs and of other NETs, including NETs originating from parafollicular C cells of the thyroid, bronchial carcinoids, thymic carcinoids, ovarian carcinoid tumours and phaeochromocytomas/paragangliomas.

2. The role of somatostatin in the diagnosis and the treatment of the gastroenteropancreatic neuroendocrine tumours (GEP NETs)

Overall, GEP NETs constitute approximately 2% of all malignant tumours of the gastrointestinal system (Moertel, 1987). Midgut carcinoids, which originate from serotonin-producing enterochromaffin cells, constitute the largest group, while the second largest group includes endocrine pancreatic tumours. Pancreatic tumours may be subdivided depending on the predominant hormone production and the clinical picture. Patients may have symptoms for many years before the diagnosis is made and therefore, in order to diagnose these tumours, the index of suspicion must be high.

During the last decade, the diagnostic and therapeutic approach of endocrine GEP tumours has considerably improved, mainly due to better imaging techniques with CT, MRI, PET and somatostatin analogue-based imaging methods, as well as receptor subtype characterisation and the introduction of long-acting somatostatin analogues.

2.1. Somatostatin receptor imaging of GEP NET

Somatostatin (somatotropin release-inhibiting hormone (SRIF)) is a peptide hormone present in two natural forms (14 and 28 amino-acids) which bind with high affinity to five different subtypes of specific somatostatin receptors (Patel et al., 1990). The very short half-life of the natural compound (around 3 min) has resulted in the development of synthetic analogues: