Diagnosis and management of neuroendocrine tumours

Dr. Ashley Grossman

Department of Endocrinology, St. Bartholomew's Hospital, London EC1A 7BE, UK

Neuroendocrine tumours (NETs) include a wide variety of rare and heterogeneous neoplasms which have varying secretory capacities and often produce distinct clinical syndromes. The term is particularly used to refer to tumours arising from secretory cells of the gastro-enteropancreatic system, either from the neuroendocrine cells in the islets of the pancreas, islet cell tumours, or from the neuroendocrine cells diffusely spread throughout the gut. These latter have been referred to loosely as 'carcinoids', but only around 10% are associated with a true carcinoid syndrome. In general, the incidence of NETs is around 30/million population/per year, making them uncommon but not especially rare.

These tumours show a wide spectrum of behaviour, from the benign small (<1cm) tumours found incidentally in inflamed appendices, through indolent carcinoids arising from the midgut, to the highly malignant small cell carcinoma of the bronchus – the 'oat cell carcinoma'. They tend to present in one of two ways: with a clinical syndrome characteristic of a secreted hormone or neuropeptide (insulinoma, gastrinoma, ectopic ACTH, etc), often early in the course of the disease process, or very late when the tumour is highly metastatic, when it may have been growing over several years or even decades. Plasma chromogranin is usually elevated, and may be used to monitor the progress of the tumour and its response to therapy. Generally, some 80-90% express somatostatin receptors, which is the basis of their identification and localisation with 111In-octretide scintiscanning; this may be used to identify the primary tumour and locate the extent of metastases. Our recent work suggests that these are particularly common in the orbit (c. 15% in our series). We have also recently shown that around 40% show uptake with the radionuclide ^{123}I-mIBG, which may be important therapeutically.

Treatment should always aim at surgical extirpation of the primary tumour, as this is likely to be the only curable procedure. When it is not, then there are a plethora of therapeutic options to improve quality of life, eradicate symptoms, and hopefully extend survival. Most important of these is the use of specific medical therapies targetted to the clinical and biochemical consequences of hormone hypersecretion. Secondly, when there is no specific anti-metabolic treatment, the presence of somatostatin receptors may allow the use of somatostatin analogues to inhibit hormone release and cause symptomatic relief. This is best effected with long-acting and well-tolerated analogues such as Sandostatin LAR or Lanreotide Autogel, every 3-6 weeks. Some patients with more non-specific symptoms, even in the absence of a clear clinical syndrome, may also show an improvement in general well-being, possibly due to modulation of other hypersecreted neuropeptides. Somatostatin analogues may also be tumouristatic in a significant minority of patients, and very rarely may be truly tumouricidal. Interferon has also been used for tumouristatic effects in patients with NETs.

With otherwise indolent tumours with good symptomatic control, no other treatment may be necessary. However, where there is positive ^{123}I-mIBG uptake, I generally consider therapy with ^{131}I-mIBG, usually giving 200 mCi every 6 months to a total dose of 1000-1200 mCi: this very well tolerated, improves symptomatic and biochemical control, and probably extends survival. A larger proportion of patients are sensitive to treatment with ^{90}Y-octreotide, and in a recent international trial this proved to be relatively free of adverse events and showed good hormonal control, with tumour shrinkage in a significant number of patients. Further work with this analogue and the newer Lu-octreotate also looks very promising.

When the tumour is clearly progressive, chemotherapy with 5FU and streptozotocin is used by many centres, while we prefer the well-tolerated combination of 5FU and lomustine; however, response rates in terms of tumour regression are only of the order of 10%. For unresponsive or faster growing tumours, etoposide and a platinum derivative are the best option. When metastases are confined to the liver but progressing, hepatic embolisation or chemo-embolisation are being increasingly used, with some recent experience of radiofrequency ablation when there are a small numbers of lesions limited in size. Partial hepatectomy has also been used, and even hepatic transplantation, but whether such heroic measures are suitable is unclear. Certainly, it is important to maintain the patients' quality of life, and use other measures such as nutritional sup-

port, adequate analgesia, localised radiotherapy where appropriate, and niacin supplementation in patients with carcinoid syndrome. The involvement of a multidisciplinary team in a centre with extensive experience offers the patient the best outcome.