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Selecting patients for cytotoxic therapies in gastroenteropancreatic neuroendocrine tumours

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A B S T R A C T

Gastroenteropancreatic neuroendocrine tumours (GEP-NET) have heterogenic clinical presentations. The majority of GEP-NET tumours have an indolent behaviour, but patients will eventually develop symptoms of tumour progression or hormone secretion that may require systemic medical interventions. Cytotoxic chemotherapy has been tested in GEP-NETs since the 80s, but treatment recommendations are controversial in many instances. Patient selection is mandatory for optimal use of chemotherapy. Important prognostic factors such as primary tumour site, tumour differentiation, tumour staging and proliferation index have been identified and validated in retrospective and prospective series. The combination of those factors and the natural history of GEP-NET provide valuable information with respect to treatment planning. In this report we provide treatment recommendations to improve systemic therapy in patients with advanced GEP-NETs based on a comprehensive review of the literature.

Introduction

Neuroendocrine tumour, historically perceived as an exceedingly rare neoplasm, has recently been shown to be more common than previously suspected. In the US SEER Registry from 2000 to 2004, the age-adjusted incidence was 5.0 per 100.000 [1]. Because these tumours derive from neuroendocrine

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cell compartments, they can arise in diverse anatomic locations. Nearly 60% of neuroendocrine tumours arise along the intestine and 15% arise in other gastro-pancreatic regions where those tumours occur less frequently such as oesophagus, stomach, appendix, colon and rectal. Close to 25% of neuroendocrine tumours arise within the bronchopulmonary system [1,2]. Those tumours and other non-gastrointestinal track tumours will be not be discussed in this report.

Gastroenteropancreatic neuroendocrine tumours (GEP-NET) are classically associated with the secretion of hormones or vasoactive peptides into the systemic circulation. Although the majority of clinical manifestations of GEP-NET often are either subtle or clinically silent, approximately 10–30% of patients have symptoms resulting from bioactive mediators secreted by these tumours [2]. These tumours are classified as 'functional' and those clinical characteristics depend on the tumour site and type of hormones secreted. In the intestine, functional tumours produce the carcinoid syndrome, mediated by serotonin secretion [3]. In pancreatic tumours the functional symptoms are related to the type of hormone secreted: gastrin, glucagon, insulin, vasoactive intestinal peptide, somatostatin or combination of them [4]. Because the pathophysiology and outcome of GEP-NETs differ substantially from gastrointestinal adenocarcinomas, clinicians must consider GEP-NET biology to select the appropriate therapy (Table 1) [1,2,4–9]. While systemic chemotherapy constitutes the backbone treatment strategy for advanced adenocarcinomas in the gastrointestinal tract, this is not the case for their neuroendocrine counterparts.

Since the 80s several systemic chemotherapy regimens have been studied and are available for the treatment of patients with indolent and aggressive GEP-NET [8,10,11]. Indication for chemotherapy use is mainly restricted to the palliative setting. Active single chemotherapeutic agents include dacarbazine, streptozocin, platinum compounds, doxorubicin, etoposide, fluorouracil, ifosfamide, irinotecan, taxanes, and temozolomide. Various combinations of chemotherapy agents have been investigated along the years and demonstrated higher response rates but at the price of higher toxicity. The data supporting doublet or triplet regimens are based on small phase II and phase III trials. The studies didn't stratify patients with advanced GEP-NET by known prognostic characteristic. Hence, clear indications for the optimal use of systemic chemotherapy are lacking and formal recommendations are still based on expert opinions [9,12–16]. For this reason, no individual treatment schema has been defined as a standard option due to insufficient data on activity and toxicity.

Table 1
Clinical presentation of GEP-NET.

Tumour	Functional symptoms	Metastases	Behaviour	OS (month) In metastatic patients
Small intestine	Diarrhoea, flushing, tachycardia, bronchospasm (carcinoid syndrome)	Frequent	Indolent disease	56
Pancreatic				
Insulinoma	Hypoglycemia, sweating, weakness, nausea	<5–12% (61% pb)	Life-threatening symptoms; Indolent disease	30
Glucagonoma	Necrotizing migratory erythema, cachexia, diabetes, deep vein thrombosis	<5% (56% pb)	Life-threatening symptoms; Indolent disease	72
VIPoma	Profound secretory diarrhoea, electrolyte disturbance	<10% (47% pb)	Life-threatening symptoms, indolent disease	60
Gastrinoma	Acid hypersecretion, abdominal pain, diarrhoea	60–90%	More aggressive	74
Somatostatinomas	Steatorrhoea, diabetes, cholelithiasis	45–78%	Indolent	40% (5y OS)*
Non-functioning	Mass effect	54%	Indolent	24
Appendix	Asymtomatic	Rare	Indolent	27
Colon	Diarrhoea, flushing, tachycardia, bronchospasm (carcinoid syndrome)	Frequent	More aggressive	5
Rectal	Mass effect	Rare	Indolent	22

* There is no clear data for median survival since somatostatinomas are rare tumours. pb: population based data.