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Anti-Tumour Treatment

A systematic review of non-surgical treatments for pancreatic neuroendocrine tumours ☆

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ABSTRACT

Introduction: Pancreatic neuroendocrine tumours (pNETs) are rare and the majority of patients present with advanced disease. Such patients have limited treatment options. We conducted a systematic review of published clinical trials of non-surgical interventions in pNET, to understand the efficacy, safety and health related quality of life (HRQoL) outcomes from the current evidence base.
Methods: Electronic databases and manual bibliographic searches were conducted to identify relevant studies. Data were extracted by two independent reviewers.
Results: Forty seven clinical studies met the predefined inclusion criteria. The following interventions were included: targeted therapies (two RCTs and six single-arm studies), chemotherapy (two RCTs, one prospective nonrandomised, comparative study and 14 single-arm studies);somatostatin analogues (SSA) and radiolabeled SSA therapies (nine single-arm studies), liver-directed therapies (six single-arm studies), mixed treatment regimens (one RCT, four single-arm studies) and other interventions such as interferon and recombinant human endostatin (one single-arm study for each). The paucity of RCT data and lack of consistency in reporting validated study outcomes and differing patient inclusion criteria between studies made it difficult to compare the relative efficacy of therapies.
Discussion: The majority of published studies assessing treatment regimens for the management of pNET are single arm, non-randomised studies, often enrolling a small number of patients and not reporting clinically meaningful outcomes. However data from recently conducted studies assessing targeted therapies indicate that it is possible to conduct adequately powered RCTs reporting standardised oncological endpoints in this rare cancer. Further, similarly robust studies should be conducted to define the optimal treatment algorithm.

Introduction

Pancreatic neuroendocrine tumours (pNETs) are rare. Worldwide, the annual incidence of pNET is estimated to range from 0.2 to 0.4 per 100,000 population, although due to the relatively indolent nature of these tumours the true prevalence may be much higher [1–3]. At presentation, 65% of patients have unresectable or metastatic disease. The 5-year survival rate of patients with metastatic disease is 30–40% and has not changed significantly over the last 30 years [4].

Clinically, pNETs are divided into two groups: functional (10–30%) or non-functional (70–90%). Functional pNETs secrete biologically active peptides, or hormones producing one of nine recognised specific hormonal syndromes. These tumours are associated with a reduced quality of life (QoL) in patients [5]. The hormones secreted by functional tumours include gastrin, insulin, glucagon, somatostatin, vasoactive intestinal polypeptide (VIP), growth hormone-releasing factor and adrenocorticotrophic hormone [5]. The hormonal syndromes are associated with diverse clinical features with regard to both metastatic potential and

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survival. For example 10% of patients who present with an insulinoma will develop metastases, compared with 50% of those with somatostatinoma and up to 70% of patients with VIPoma [6].

Surgery, where possible, is considered the first-line treatment for pNET patients. Due to the presence of distant metastatic disease or local extension of the tumour, surgery is often non-curative, but even in advanced cases surgical debulking of disease can reduce symptoms related to tumour burden and hormone production [7]. For patients who are not candidates for surgery, the choice of treatment depends on the stage of the disease, symptoms and histological features of the tumour [8]. Treatment options include SSA and liver-directed therapies (for example, chemoembolisation, radioembolisation, arterial embolisation and radiofrequency ablation, which are palliative options for liver-dominant disease) [6,7,9–11]. In clinical practice, systemic chemotherapy is commonly used in the treatment of pNET, but with modest efficacy (responses are rarely complete) and the attendant toxicity profiles. Such chemotherapy agents include streptozocin, doxorubicin, 5-fluorouracil, dacarbazine, capecitabine and temozolomide [6,7,9,12].

There have been limited developments in the management of advanced pNET over the last two decades [13,14]. However, an improved understanding of the molecular mechanisms underlying pNET has led to more recent treatment options that include agents directed at inhibiting growth factors or their receptors that are produced by these tumours [15,16]. Several of these agents are still investigational and to date, only the tyrosine kinase inhibitor sunitinib and the mTOR inhibitor everolimus have been licensed by the European Medicines Agency and the FDA for the treatment of unresectable or metastatic, well-differentiated pNETs with disease progression in adults.

A number of reviews of treatments specifically for pNET have been previously published [7,15,17], as well as reviews of treatments for all NETs [12,18–20]. Several evidence-based guidelines on the management of pNET are available which include recommendations for the treatment of pNET (e.g. guidelines from the UK and Ireland Neuroendocrine Tumour Society (UKINETS) [6], the National Comprehensive Cancer Network (NCCN) [21] and the European Neuroendocrine Tumour Society (ENETS) [9].

More recently, key recommendations from the NET Clinical Trials Planning Meeting included the separate examination of carcinoid tumours and pancreatic NETS in clinical trials and the avoidance of SSA washout periods when evaluating novel agents for the control of hormonal syndromes [22]. An update to the UKINETS guidelines covers genetics, diagnosis, imaging, pathology, treatment, ablation and carcinoid heart disease [23]. Updated consensus guidelines from ENETS are also available [24].

As new targeted therapies emerge and become more widely used in the management of pNET, this review was undertaken to understand the current evidence base in terms of efficacy and safety of non-surgical treatments and to assess the trial methodology supporting the use of chemotherapies and new agents in this setting.

Methods

Inclusion criteria

Randomised controlled trials (RCTs), non-RCTs and prospective single-arm studies were included if they enrolled adult patients with a confirmed diagnosis of pNET (as defined by recognised clinical guidelines). Studies enrolling patients with NETs of any aetiology (including pancreas) were included as long as relevant efficacy/safety outcomes were reported for the pNET subset of patients. Only studies with at least 10 pNET patients were included in

Table 1
Inclusion and exclusion criteria.

Criterion	Included	Excluded
Population	• Age: ⩾18 years • Race: any • Qualifying disease: pancreatic neuroendocrine tumours (pNET)† • No restriction on previous treatment/surgery (ie treatment naïve & refractory patients)	• Age:⩽18 years• Non-pancreatic neuroendocrine tumours
Perspective of study	• Prospective (concurrent) • Comparative • Non-comparative	• Retrospective
Study characteristics	RCTs: parallel/Cross-over design (with adequate wash-out period between treatments Non-RCTs: cohort/case series	• Case report• Case studies with single patient
Language	• Any	-
Trial length	• All study durations	-
Sample size	• ⩾10 pNET patients	• <10 pNET patients
Interventions/ treatments	• Systemic chemotherapy • Targeted therapies (including everolimus, bevacizumab, sorafenib, sunitinib, gefitinib) • Somatostatin analogue • Interferon/Biotherapy • Radionuclide therapy, including peptide receptor radionuclide therapy • Radiofrequency ablation • Chemo-embolisation • Hepatic artery embolisation (HAE) with/without chemotherapy (HACE) • Combination regimens. • No restriction on dose, formulation, or mode of delivery	• Surgery
Control intervention/ treatments	• Any of the interventions listed abovePlacebo/usual careNo treatment	-
Included trial outcomes	*Efficacy*, including but not restricted to overall survival, progression free survival, objective overall response rate (PR + SD), Time to progression (TTP)/duration of response *Safety*, including withdrawals due to: • Any reason • Lack of efficacy • Adverse events • *Health-related quality of life*	Studies only reporting symptomatic relief outcomes for functioning tumours

AE, adverse event; PR, partial response; RCT, randomised controlled trial; SD, stable disease.
† Studies enrolling patients with neuroendocrine tumours of any aetiology (including pancreas) were be included as long as relevant efficacy/safety outcomes were reported for the pNET subset of patients.