Review

Advances in the treatment of pancreatic neuroendocrine tumours

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Summary

Pancreatic neuroendocrine tumours (pNETs) are relatively rare and generally felt to follow an indolent course. But poorly differentiated tumours can behave aggressively with 5-year survival ranging from 31% to 48%. Recent data suggest that patients with pNETs may derive benefit from treatment targeting the molecular changes expressed in this tumour group. This article describes advances in the treatment of unresectable pNETs that have led to a doubling of progression free survival.

Introduction

Pancreatic neuroendocrine tumours (pNETs) can be categorized into two broad groups: the functional pNETs that are associated with clinical syndromes due to ectopic secretion by the tumour of biologically active substances, and non-functional pNETs. Functional pNETs include insulinomas, gastrinomas, VIPomas, somatostatinomas and glucagonomas.1

Unfortunately, the majority of these tumours present late, but when diagnosed in the absence of metastases may be cured by surgical resection.2 Liver metastases are common in patients with pNETs, and hepatic resection or embolization represents potential treatment options.3 Chemoembolization, where intra-arterial cytotoxic chemotherapy is added to embolization, has been reported to improve outcomes for patients with pNETs.4 Liver transplantation is occasionally considered in unresectable hepatic disease but has limited application.5

In the ontology of treatment, somatostatin analogues or Interferon-α have become standard medical therapies to treat tumour-associated symptoms, suppressing hormone production but not acting to reduce tumour mass.6 Streptozocin-based chemotherapy has been the mainstream systemic chemotherapy treatment for pNETs, and, unlike somatostatin analogues or interferon, is associated with objective tumour responses in 30–40% of patients for a duration of response ranging from 9 to 28 months.7–9 The side effects of streptozotocin chemotherapy are generally mild but significant. More recently, oral temozolomide-based regimens have been shown to be associated with overall response rates comparable to streptozotocin, with the added advantage of less toxicity, confined to anaemia and thrombocytopenia.10,11
Well-differentiated pNETs contrast in their poor response to standard chemotherapy as compared with poorly differentiated tumours. This differential response is thought to be a reflection of lower mitotic rates and higher levels of bcl-2 and the multi-drug resistance gene. But this apparently poorer prognosis, arising from the molecular characteristics of well-differentiated pNETs, is part of a complex story, an understanding of which has been translated into new treatments for pNETs. Well-differentiated pNETs are highly neo-vascularized tumours, with increased expression of several angiogenesis-related receptors including those for epidermal growth factor (EGF), platelet-derived growth factor (PDGF), insulin growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF). Growth factor expression leads to an opportunity for a chance of a response to the small-molecule tyrosine kinase inhibitors (TKIs) including sorafenib, pazopanib and sunitinib that target these receptors.

New treatments

Sunitinib

Sunitinib is an oral, multi-target receptor TKI, which competes with ATP for binding within the intracellular domain of platelet-derived growth factor receptor (PDGFR)-α and PDGFR-β, VEGFR, stem cell factor receptor (c-KIT), FMS-like tyrosine kinase-3, glial cell-line-derived neurotrophic factor receptor rearranged during transfection (RET) and the receptor of macrophage-colony stimulating factor 1. Sunitinib is currently licensed for the use in metastatic renal cell carcinoma and for the treatment of unresectable or metastatic malignant gastrointestinal stromal tumour after the failure of treatment with imatinib mesylate (Figure 1).

Cellular activity

Sunitinib has been shown to reduce tumour burden in the rat insulin promoter (RIP1)-Tag2 transgenic mouse model of pancreatic islet cell carcinoma by inhibiting proliferation of the VEGFR-dependent endothelial cells and by reducing the PDGFR-dependent pericyte coverage.

Patients

Sunitinib was initially shown to be active in a Phase I study where four neuroendocrine tumour patients showed responses, leading to the launching of a Phase II multicentre trial for advanced pancreatic islet cell cancer patients. In this group the response rate was impressive, with 56.1% of patients having tumour stabilization for >6 months. Objective responses were described in 16.7% of patients. Side effects were generally mild but included a significant risk of gastrointestinal haemorrhage, a known consequence of VEGFR inhibition.

In a third study, 171 patients with well-differentiated pNET were randomized to receive either sunitinib or placebo. This study ended early because the primary end point of the study was met, with a dramatic advantage for sunitinib over placebo. Progression-free survival was doubled in sunitinib-treated patients compared to placebo. The probability of progression-free survival at 6 months was 71.3% in the sunitinib group and 43.2% in the placebo group.

Everolimus

Cellular activity

Treatment with everolimus targets the intracellular serine/threonine protein kinase mammalian target of rapamycin (mTOR) that mediates multiple downstream signalling pathways integrating IGF-1, EGF and VEGF. Autocrine activation of the mTOR signalling pathway, mediated through insulin-like growth factor 1, has been implicated in the proliferation of pNETS and inhibition of mTOR has been shown to have significant anti-proliferative effect on pNET cell lines (Figure 2).

Patients

In a Phase II study, 60 neuroendocrine tumor patients were randomly assigned to receiving 5 or 10 mg of everolimus daily in combination with octreotide. Objective responses were seen in 27%
of patients and stable disease in 60%. The progression-free survival was 50 weeks. Treatment was generally well tolerated. This study demonstrated that everolimus is effective and well tolerated in the treatment of low-grade to intermediated-grade pNETs.28

In a third study, 160 pNET patients were randomized to receive everolimus alone or everolimus plus octreotide long acting release (LAR). Overall response rates were low at 4–9%, but a significant proportion of patients, up to 80%, had stable disease. Progression-free survival was 16.7 months with combination therapy and 9.7 months with everolimus as a single agent. It was not possible to conclude, however, if combination is better than everolimus alone from the design of this study. Adverse reactions were generally mild and tolerable.29

Because many patients with pNETS fortunately experience long periods without disease progression, an opportunity was sought to investigate treatment in patients with progressive disease.30 Four hundred and ten patients were recruited in an international multicentre Phase III trial, who had exhibited radiological progression within the preceding 12 months. The median progression-free survival was 11.0 months with everolimus as compared with 4.6 months with placebo. Objective tumour responses were seen in just 5% of patients receiving everolimus and surprisingly also in 2% of placebo groups. The primary benefit from everolimus was in disease stabilization or minor tumour shrinkage. The most significant drug toxicity specific to everolimus was upper respiratory, and included non-infectious pneumonitis and interstitial lung disease. Atypical infections such as pulmonary tuberculosis, bronchopulmonary aspergillosis and reactivation of hepatitis B were also observed with everolimus therapy. There was one treatment-related death from acute respiratory distress syndrome in one patient with insulinoma in the everolimus group.

Conclusions

Until now, treatment options for patients with unresectable pNET have had limited impact on disease progression and survival. Sunitinib is the first-targeted therapy to be licensed for this disease and represents a new treatment option for this area of unmet medical need. The effectiveness and safety profile of TKI in comparison to standard chemotherapy has paved the way for other target-based therapeutic approaches and has changed our current approach to the management of other pNETs.

Conflict of interest: None declared.

References


