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SHORT REVIEW

Sunitinib Efficacy in Advanced Pancreatic Neuroendocrine Tumors

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Abstract: Pancreatic neuroendocrine tumors (PNETs) are relatively rare and generally considered to follow an indolent course. However poorly differentiated or metastatic PNETs can also behave in an aggressive manner with a 5-year survival as low as 30% in non-functioning PNETs. Many therapeutic agents have been tested in the treatment of NET including Interferon alfa, streptozocin or temozolomide-based combination chemotherapy with an objective response of 10%–30%. Moreover these agents are less effective in patients with advanced carcinoid tumors and their prolonged use is often associated with added toxicity. A number of other signaling pathways have also been implicated in neuroendocrine tumors, which also express platelet-derived growth factor (PDGF), PDGF receptor (PDGFR), insulin-like growth factor-1, insulin-like growth factor receptor, basic fibroblast growth factor, transforming growth factor, epidermal growth factor receptor, and stem-cell factor receptor.
Sunitinib malate (SUTENT®; Pfizer Oncology) is a small molecule kinase inhibitor with activity against a number of tyrosine kinase receptors, including VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α, PDGFR-β, stem-cell factor receptor, glial cell line derived neurotrophic factor receptor and FMS-like tyrosine kinase-3.
This review will present data regarding sunitinib progress in PNET, demonstrating its effectiveness and the emerging hope it may provide for such a disease with limited treatment options.

Keywords: sunitinib, neuroendocrine, VEGFR, PDGFR, efficacy

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Introduction

Pancreatic neuroendocrine tumors (PNETs) are relatively rare and generally considered to follow an indolent course. However, poorly differentiated or metastatic PNETs can also behave in an aggressive manner with a 5-year survival as low as 30% in non-functioning PNETs.[1] The most common presentation is the carcinoid syndrome, which is associated with high serotonin levels, episodic flushing, diarrhea, and right-sided valvular heart disease.[2,3] When neuroendocrine tumors are diagnosed at an early stage, surgical resection is often curative.[4] However palliative options for patients with advanced neuroendocrine tumors are limited.

Approximately 90% of neuroendocrine tumors express somatostatin receptors.[5] Although somatostatin analogs are effective in ameliorating hormonal secretion symptoms, they rarely result in tumor regression.[6,7]

Many therapeutic agents have been tested in the treatment of NET including interferon alfa, streptozocin or temozolomide-based combination chemotherapy with an objective response of 10%–30%.[8–12] Moreover, these agents are less effective in patients with advanced carcinoid tumors and their prolonged use is often associated with greater toxicity.[13]

The highly vascular nature of neuroendocrine tumors led to initial interest in angiogenesis inhibition as a treatment modality.[14] Overexpression of vascular endothelial growth factor (VEGF), together with VEGF receptor (VEGFR) subtypes, has been observed in both carcinoid and pancreatic endocrine tumors, suggesting that autocrine activation of the VEGF pathway may promote tumor growth.[15–17]

A number of other signaling pathways have also been implicated in neuroendocrine tumors, which also express platelet-derived growth factor (PDGF), PDGF receptor (PDGFR), insulin-like growth factor-1, insulin-like growth factor receptor, basic fibroblast growth factor, transforming growth factor, epidermal growth factor receptor, and stem-cell factor receptor.[18–26]

Sunitinib malate (SUTENT®; Pfizer Oncology) is a small molecule kinase inhibitor with activity against a number of tyrosine kinase receptors, including VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α, PDGFR-β, stem-cell factor receptor, glial cell line-derived neurotrophic factor receptor and FMS-like tyrosine kinase-3.[27–30]

Sunitinib antitumor activity was reported in patients with renal cell carcinoma (RCC) and GI stromal tumors (GIST) and subsequent trials in both RCC and GIST confirmed antitumor activity and safety in these tumor types.[31–34] This led to approval by the US Food and Drug Administration (FDA) in January 2006 and the European Medicines Agency (EMEA) in October 2006 for use in advanced RCC patients as a first line of therapy and in GIST patients after disease progression on, or intolerance to, imatinib therapy. (http://www.fda.gov and http://www.ema.europa.eu).

This review will present the data regarding sunitinib progress in PNET demonstrating its effectiveness and the emerging hope it may provide for such a disease with limited treatment options.

Natural History of the Disease

PNETs have long been considered to be rare as far as pancreatic neoplasms are concerned. Surveillance, Epidemiology and End Results (SEER) data reports an incidence of 1.4%, with a far better overall prognosis and long term survival as compared to cancer arising from the exocrine pancreas.[35] Interestingly, autopsy studies suggest that although not clinically apparent, the incidence may actually be higher; up to 10%.[36]

A recent epidemiological study reports a greater prevalence of neuroendocrine tumors than previously reported. Using SEER data from 1973–2004, a significant increase in age-adjusted incidence was found: 1.09 per 100,000 inhabitants in 1973 to 5.25 per 100,000 inhabitants in 2004 (Fig. 1). For those tumors which originate in the pancreas, the incidence was reported to be 0.32 per 100,000 from 2000–2004, with a median age of 60 years at diagnosis. These tumors are generally felt to be more slow-growing and indolent than other malignancies, but in the analysis only 14% of patients presented with localized disease, 22% with regional involvement and 64% with distant metastases.[37]

Standard medical therapy aims to treat symptoms of these tumors with somatostatin analogues or interferon alpha. Somatostatin analogues result not only in the palliation of symptoms, thereby improving the quality of life.[38] Therefore, octreotide remains the mainstay of treatment for these tumors. In addition Streptozosin, adriamycin, 5-FU and dacarbazine have been used both as single agents and in combination,

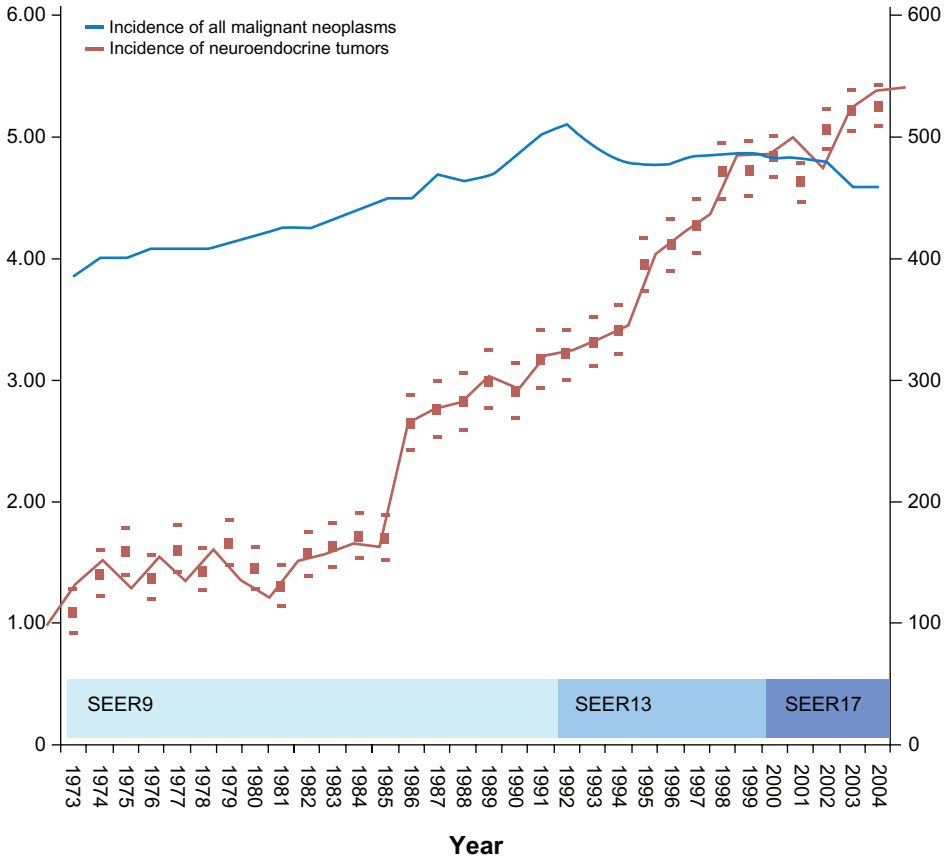

Figure 1. Incidence per 100,000 for neuroendocrine tumors using SEER data.
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with streptozosin/doxorubicin as the recommended regimen.[39]

Well-differentiated PNETs have been found to have a poor response to chemotherapy as compared to poorly differentiated tumors. This is thought to be related to low mitotic rates (the majority of patients with a Ki-67 of less than 2% in the PROMID study), high levels of bcl-2 and higher expression of the multidrug resistance gene.[40] A study of cisplatin/etoposide was associated with a 67% response rate for poorly-differentiated tumors with little activity in well-differentiated tumors, making this an option for those less differentiated cases.[41]

Temozolomide has been also studied as an option based on the activity seen with dacarbazine, as they both share an active metabolite. Responses have been reported for PNET tumors with lower levels of O-6-methylguanine- DNA methyltransferase (MGMT) expression with one study describing deficiency of MGMT expression in 51% of pancreatic neuroendocrine tumor samples, and 34% of these demonstrating a partial or complete response to temozolomide based regimens.[42]

Sunitinib in PNETs: The Rationale and the Efficacy

As previously mentioned PNETs have increased expression of several receptors, including those for EGF, PDGF, insulin-like growth factor (IGF)-1 and VEGF. In the RIP1-Tag2 transgenic mouse model of pancreatic islet cell carcinoma, sunitinib reduced tumor burden and increased median animal survival (18.8–24 weeks) by inhibiting the proliferation of VEGFR-dependent endothelial cells and by reducing the PDGFR-dependent pericyte coverage (P value = < 0.05).[43]

Among three patients with advanced neuroendocrine tumors who entered in the phase I trials primarily referred for tumor progression after several lines of chemotherapy, one exhibited an impressive partial response and two others experienced sustained tumor stabilizations.[44] This potential efficacy has paved

the way for the investigation of sunitinb in PNETs (Table 1).

Sunitinib in phase II trial: the potential role

Based on the above-mentioned results; Kulke et al Performed a multicentre phase II study in which 107 patients (carcinoid n = 41; pancreatic n = 66) were enrolled at 8 centres in the United States between March 2003 and November 2005 in order to assess the safety and efficacy of sunitinib in patients with advanced neuroendocrine tumors. Eligible patients (treatment with prior chemotherapy, embolization, or radiotherapy was permitted and patients receiving stable doses of somatostatin analogs were allowed to continue receiving these treatments) with carcinoid and pancreatic endocrine tumors received repeated 6-week treatment cycles of sunitinib administered at an oral dose of 50 mg once daily for 4 weeks, followed by 2 weeks off treatment. However, patients who had prior treatment with VEGF pathway inhibitors, known brain metastases, a history of cardiac arrhythmias, or evidence of myocardial ischemia or cerebro-vascular accident within 12 months were excluded.[45] Radiologic response was chosen as a primary end point of the study and patients were also observed for time to response/progression, survival, toxicity, reported outcomes and drug exposure levels.

The results of this study showed that: overall objective response rate (ORR) in pancreatic endocrine tumor patients was 16.7% (11 of 66 patients), and 68% (45 of 66 patients) had stable disease (SD). Among the carcinoid patients, ORR was 2.4% (one of 41 patients), and 83% (34 of 41 patients) had SD. Median time to tumor progression was 7.7 months in pancreatic neuroendocrine tumor patients and 10.2 months in carcinoid patients. One-year survival rate was 81.1% in pancreatic neuroendocrine tumor patients and 83.4% in carcinoid patients.[45]

In both populations no significant differences from baseline in patient-reported quality of life or fatigue were observed during treatment. The toxicity profile of sunitinib in this study was similar to that observed in trials of sunitinib in other disease types. The most common treatment-related toxicities were

Table 1. Selected clinical trials investigating sunitinib in pancreatic neuroendocrine tumors.

Trial	Phase	Study group	Enrolment status	Primary outcome
NCT01121562*	Phase II	Progressive Advanced/ metastatic well-differentiated pancreatic neuroendocrine tumors	Ongoing, but not recruiting participants	Clinical benefit response rate is defined as the percent of patients with CR, PR or SD with time to treatment failure ≥24 weeks according to the RECIST guidelines, relative to the total analysis population
NCT00428597*	Phase III	Patients with progressive advanced/metastatic well-differentiated pancreatic islet cell tumors	Terminated	Progression free survival (PFS)
NCT00434109*	Phase II	Sunitinib malate following hepatic artery embolization for metastatic gastrointestinal neuroendocrine tumors	Ongoing, but not recruiting participants	Progression-free survival rate at 12 months after first embolization
NCT01215578*	Phase II	Patients with poorly-differentiated advanced/ inoperable NEURO-endocrine tumors	Currently recruiting participants	Predictive molecular markers of response to sunitinib
NCT00444795*	Phase IV	Well-differentiated advanced and/or metastatic pancreatic neuroendocrine carcinoma	Enrolling participants by invitation only	To monitor use in real practice including adverse events on SUTENET capsules (sunitinib malate)
NCT00813423*	Phase I	Patients with advanced solid tumors that have not responded to chemotherapy	Currently recruiting participants	Studying the side effects and best dose of sunitinib when given together with hydroxychloroquine

Note: *www.clinicaltrials.gov (last accessed April 2011).

constitutional (fatigue and anorexia) or GI (diarrhea and nausea). Hypertension, a toxicity also observed with other inhibitors of the VEGF pathway, was observed in 15.9% of the patient population. It is worth noting that hypertension was more common in carcinoid patients than in patients with PNETs (19.7% *vs* 9.8%, respectively), a finding possibly related to concurrent secretion of vasoactive neuropeptides in some carcinoid patients. A higher incidence of grade III leucopenia in PNETs patients than in patients with carcinoid cancers (18.2% *v* 7.3%, respectively) may be attributable to the greater number of PNET patients who had received prior systemic therapy, including cytoxic chemotherapy.[45]

Kulke et al concluded that treatment with sunitinib resulted in objective tumor responses in patients with pancreatic neuroendocrine tumors. Sunitinib may also be associated with an antitumor effect in carcinoid tumors, but this could not be clearly determined in this non-randomized study. Further investigation of sunitinib in the randomized setting or in combination with other agents is warranted in these diseases.

Sunitinib in phase III trial: the proved efficacy

It was evident that the promising results from the phase II trial conducted by Kulke et al had set the fundamental basis for the launching of a larger phase III randomized trial.

A large phase randomized, double-blind placebo controlled phase III trial was launched to evaluate the efficacy and safety of sunitinib vs. placebo in patients with advanced well differentiated PNETs who had a disease progression within 12 months prior to enrolment.[46] Patients meeting the eligibility criteria were enrolled between June 2007 and April 2009. Median PFS was 11.4 months in patients receiving sunitinib vs. 5.5 months in the placebo arm ($P = 0.0001$). The objective response rate with sunitinib was 9.3% (95% CI: 3.2% to 15.4%), including 2 complete responses and 6 partial responses, vs. 0% in the placebo arm ($P = 0.0066$). Overall survival was improved with sunitinib (HR: 0.409; $P = 0.0204$). The trial enrolled 171 patients with well-differentiated PNETs with disease progression in the prior year and they were randomized to receive sunitinib 37.5 mg/day (86 patients) or placebo (85 patients). Overall, 95% of patients had distant metastases, 89% had prior surgery, and about half received prior chemotherapy (52% in the sunitinib arm, 59% in the placebo arm).

Approximately 25% of patients received prior somatostatin analogs (24% sunitinib arm, 22% placebo arm). In this study, 49% of patients had functioning tumors. Because the study was terminated early, median overall survival was not reached. However, median progression free survival was found to be significantly longer in the group treated with sunitinib (11.4 months versus 5.5 months) with fewer adverse events (leucopenia, hand and foot syndrome, hypertension and neutropenia ranging from 6%–12% in the sunitinib-treated arm).[46]

In the same trial, the investigators tried to assess the patient reported tolerability of the sunitinib arm by using a quality of life questionnaire. Overall, 73 out of 86 patients in the sunitinib group and 71 out of 85 patients in the placebo group were evaluable. Data were obtained on day 1 of every 4 week cycle, and data from the first 10 cycles were analyzed. Although diarrhea and insomnia seemed to be statistically worse in the treatment group, quality of life scores did not show clinical or statistically significant differences. Thus, sunitinib appears to be a viable treatment option in terms of patient tolerability.[47]

A sub group analysis was performed in order to determine whether there are certain patient characteristics, which might predict a better response to sunitinib therapy. The parameters evaluated were age (less than 65 years versus more than, or equal to, 65 years), race (caucasian or not), gender, performance status (Eastern Cooperative Oncology Group (ECOG) 0 compared to 1 and 2), number of sites of metastatic disease (2 or less versus 3 or more), and time from diagnosis to enrolment in study (more than 3 years versus 3 or less). All groups benefited in terms of progression free survival. Prior therapy did not have an effect on response to treatment. For the analysis, 72 patients had Ki-67 values available, and for those with Ki-67 index equal to, or less than 5%, there was a progression-free survival improvement with a hazard ratio (HR) of 0.378 ($P = 0.0259$).[48]

Conclusion

It is likely that sunitinib (SUTENT®; Pfizer) demonstrates efficacy in PNETs thereby leading to the conclusion that sunitinib is a viable treatment option

in all patients with advanced well-differentiated pancreatic neuroendocrine tumors. It is evident that sunitinib will pave the way for further trials in other neuroendocrine tumor types such as carcinoids, poorly-differentiated neuroendocrine diseases, and several other endocrine tumors which are dependent on VEGF/VEGFR for angiogenesis. With other distinct mechanisms of action, such as mTOR inhibitors, which are currently being investigated in phase III trials, multiple medical options to control tumor growth and metastasis will be offered to patients in a disease that was thought to have limited choices.

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Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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