Latest advances in pancreatic neuroendocrine cancer

HOT SPOT

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Background

- Pancreatic Neuroendocrine (pNET) cancers are uncommon malignancies arising from the endocrine cells of the pancreas
- Annual incidence is one per 100,000
- Incidence and prevalence are increasing
- pNETs may be under-diagnosed and are often diagnosed late
- Approximately 2/3 of patients present with metastatic disease
- pNETs can be "functionally" active secreting a variety of hormones such as insulin, glucagon, gastrin, serotonin, and vasoactive intestinal peptide with associated syndromes
- Most PNETs are "non-functioning"

Historical treatment options

- Surgery remains the only curative treatment option
- Liver direct treatment can also be useful and may include embolization as well as tumour debulking surgery
- Previous systemic treatment options were limited to streptozocin-based chemotherapies (given with either 5FU or doxorubicin)
- Older studies have reported response rates (RR) to streptozocin-based chemotherapy as high as 69%. However, these studies used older criteria for response such as physical examination
- Toxicity is significant with streptozocin-based treatment including nausea, vomiting and bone marrow toxicity, as well as renal impairment
- More recent studies have been unable to reproduce such high RR
- Currently there is debate regarding the role of streptozocin-based chemotherapy considering the questionable response rates and high toxicity
- Streptozocin is not available on the Canadian open market at present time and needs to be imported into Canada, making access to the drug difficult

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Newer treatment options

Temozolomide

- The oral alkylator temozolomide has shown activity in treating metastatic pNETs
- Temozolomide is converted to the active alkylating agent MTIC through spontaneous conversion
- A phase II trial showed the combination of temozolomide and thalidomide had RR of 45% in metastatic pNETs
- A single arm study of 30 chemotherapy naïve patients with metastatic, well or moderately differentiated pNETs showed an RR of 70% with the following chemotherapy regimen:
  - Capecitabine (750mg/m^2) bid × 14d with temozolomide 200mg/m^2 daily, days 10–14
- Common grade 3 and 4 toxicities included elevated AST/ALT (3%), leukopenia (3%) and thrombocytopenia (3%)
- Temozolomide is a promising agent in pNETs and further investigation is warranted in randomized trials

Sunitinib (Sutent)

- pNETs are considered to be hypervascular tumours and often have a typical hypervascular pattern on radiological imaging
- Vascular endothelial growth factor (VEGF) plays an important role in angiogenesis in pNETs
- Sunitinib is known to inhibit VEGF2 and VEGF3, as well as other kinases
- Sunitinib has previously shown activity in mouse models, as well as phase 1 and 2 trials in patients with pNETs
- Sunitinib has now been shown to be effective in treating pNETs in a recently published large, multinational, randomized, double-blinded, placebo controlled phase 3 trial (n=171)
- Patients enrolled had well-differentiated pNETs with documented disease progression in the last 12 months and had either locally advanced or metastatic disease not eligible for surgery
- Most of the patients had been previously treated with systemic chemotherapy
- This trial was discontinued early by independent data and safety committee due to the effect of the drug
- Dosage administered was 37.5 mg po daily continuously with patients on the study drug on treatment for a median of 4.6 months (range 0.4 to 17.5 months)
- Median progression-free survival (PFS) was 11.4 months in the sunitinib group versus 5.5 months in the placebo group (HR=0.42, p<0.0001) (Figure 1)
- Objective response rate (complete response + partial response) was 9.3% in the sunitinib arm versus 0% in the placebo arm
- Hazard ratio for death was 0.41 (p=0.02) in favour of sunitinib before study closure and crossover. Post-crossover median overall survival (OS) for sunitinib and placebo was 30.5 months versus 24.4 months respectively (p=0.1926)
- Most common grade 3 and 4 toxicities were neutropenia (12%), hypertension (10%) and hand-foot syndrome (6%), as well as diarrhea, fatigue and asthenia (all 5%)
- Based on these results sunitinib has received Health Canada approval for use in unresectable pNETs

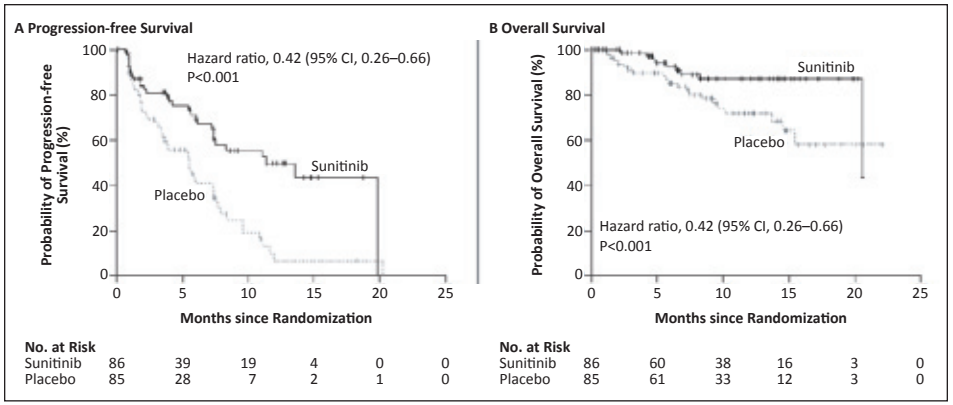

Figure 1.

Everolimus (Afinitor)

- Mammalian target of rapamycin (mTOR) signalling pathway has been shown to be involved in the proliferation of pNET tumour cells (mediated through insulin-like growth factor pathway)
- Everolimus is an mTOR inhibitor and has shown promising activity in two Phase 2 cells involving pNETs
- Everolimus was tested in a large (n=410), multicentre, double-blinded, placebo-controlled, phase III study with crossover design
- Patients enrolled had low or intermediate grade unresectable or metastatic pNETs with radiological documentation of progressive disease in the last 12 months
- 50% of patients had received prior chemotherapy, and there was no difference in median progression-free survival (PFS) between those who received chemotherapy and those who did not
- Everolimus was administered at a dosage of 10mg daily with median duration of treatment of 8.79 months (range 0.25 to 27.47)
- Primary end point of the trial was PFS and was 11.0 months in the everolimus arm versus 4.6 months in the placebo arm (HR=0.35, p<0.001) (Figure 2)
- Most common grade 3 and 4 toxicities were stomatitis (7%), hyperglycemia (5%), anemia (6%) and thrombocytopenia (4%)
- Based on these data, everolimus was approved by the FDA for unresectable pNETs and awaits Health Canada approval

Multidisciplinary care

- Surgical and systemic treatments are often complementary in the treatment of pNETs and all neuroendocrine cancers (NETs)
- Previous studies have shown improved outcomes in NETs patients with multidisciplinary care
- A unique integrated NETs clinic has been established at Sunnybrook Odette Cancer Centre
- The Sunnybrook NETs clinic is patient-centric with integrated care patterns and access to new treatments (Figure 3)
- Patients at this clinic have access to both medical and surgical oncology at the same visit, as well as specialty nursing care

Future trends

- pNETs is an uncommon malignancy, but is increasing in incidence
- Options in the treatments of pNETs have expanded recently with many new exciting options including temozolomide, as well as the biological agents sunitinib and everolimus
- With many new treatment options, the optimal first-line treatment for pNETs is unknown (chemotherapy versus biologic and if biologic, which one)
- Further trials are needed to determine the optimal order of treatments for NETs and may involve biomarker investigations to help individualize treatments
- Multidisciplinary care is going to become an increasingly important part of treatment of pNETs

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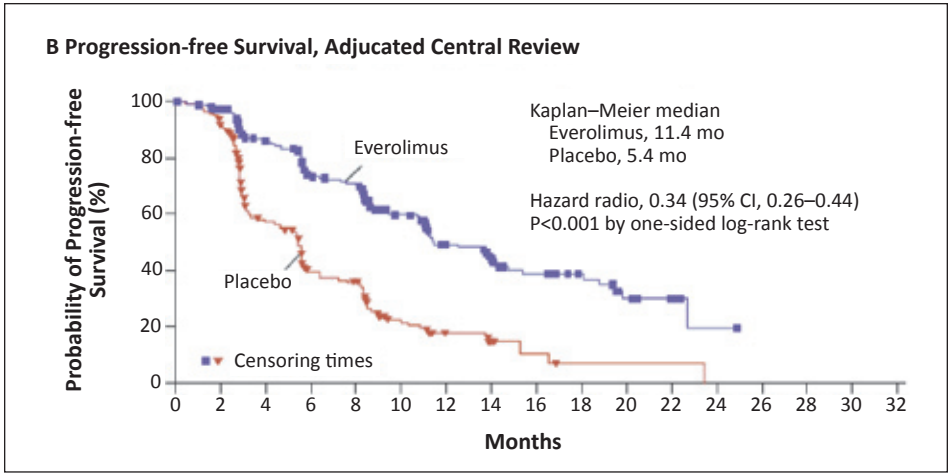

Figure 2.

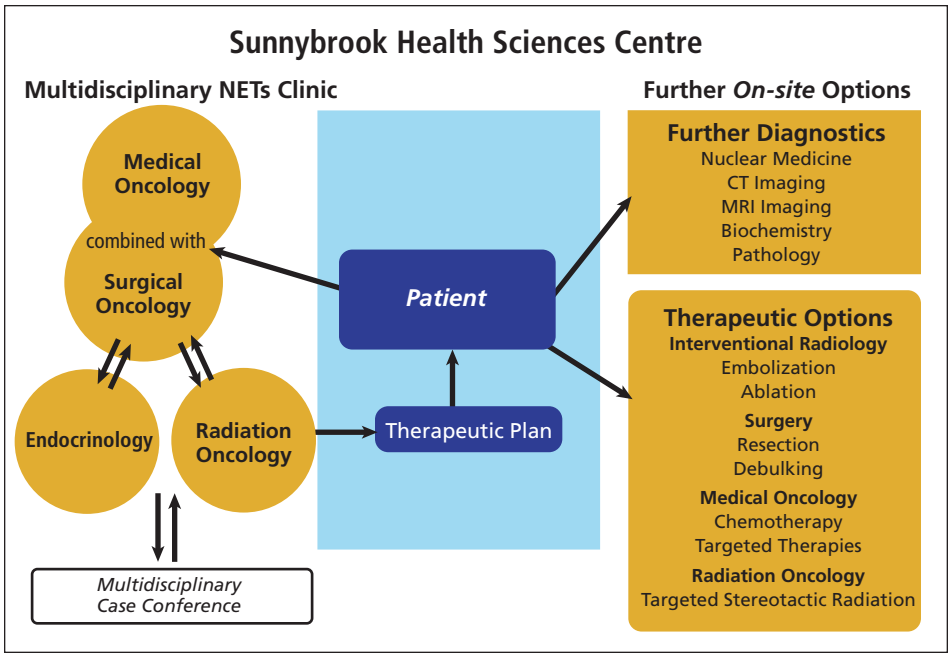

Figure 3.