CHAPTER 8

Systemic therapies: Somatostatin analogues and targeted agents

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Practice Points

- A benefit from somatostatin analogue (SSA) therapy may be predicted by somatostatin scintigraphy.
- It may be useful to initially commence patients on a short acting SSA to assess treatment tolerability before converting to a long acting preparation.
- The recommended starting dose as per the trials evidence when used for an anti-proliferative effect is Octeotide LAR 30mg or Lanreotide 120mg every 4 weeks.
- In patients with carcinoid symptoms worsening despite SSA treatment, a common practice based on anecdotal experience is to trial increasing the frequency of administration of long acting agents (e.g. every 3 weeks rather than 4 weekly). However only standard dose therapy is reimbursed by the PBS.
- Long-acting SSA therapy should be withheld at least four weeks prior to somatostatin scintigraphy. Patients who are intolerant of an interruption of SSA therapy may be managed with short-acting agents, which can be ceased close to the time of the scan.
- Whilst many patients with NENs report diarrhoea secondary to carcinoid syndrome or malabsorption due to prior surgery, octreotide treatment is known to induce diarrhoea and has been reported to cause pancreatic insufficiency and steatorrhea. A trial of supplemental pancreatic enzymes (Creon) can be effective in these patients.
- The decision to use targeted therapies, chemotherapy or peptide receptor radionuclide therapy (PRRT) after failure of SSA is complex and is subject to current ongoing trials. Patients should ideally be referred for discussion to a specialist NEN MDT where possible, particularly if PRRT is being considered.
- Sunitinib and Everolimus have not been compared in any large trial in pancreatic NETs and the selection of either should be based on the patients' history and side effect profile. For example in those patients with poorly controlled hypertension, Everolimus may be more suitable and alternatively in those patients with poorly controlled diabetes, Sunitinib may be more appropriate.

1. Short and Long Acting Somatostatin Analogues (SSA)

Somatostatin analogues (SSAs) are considered first-line therapy in patients with unresectable or metastatic well or moderately differentiated gastroenteropancreatic neuroendocrine neoplasms (NENs). SSAs have two main uses in NENs. Firstly, control of symptoms related to hormone excess produced by functionally active NENs (otherwise known as carcinoid syndrome) and secondly to slow the progression of disease via an anti-proliferative effect.

1.1 Amelioration of symptoms of carcinoid syndrome

The effectiveness of long acting SSAs to ameliorate the symptoms of carcinoid syndrome was published over 30 years ago (1). Improvement of symptoms such as diarrhoea and flushing has been reported in around 70-90 percent of those patients treated with SSAs. The Australian Pharmaceutical Benefits Scheme (PBS) subsidises short acting SSA Octreotide and long acting SSA Octreotide and Lanreotide for functionally active gastroenteropancreatic NENs under specific conditions as listed on the Australian PBS website. Octreotide and Lanreotide are considered equally as effective in ameliorating the symptoms of functionally active NENs but have not been directly compared in any large prospective trial. Refer to Chapter 7: "Functional neuroendocrine neoplasms" for further details.

1.2 Anti-proliferative effects

In addition to symptomatic improvement, there is strong evidence that SSAs also have anti-proliferative activity in neuroendocrine neoplasms.

In the phase III CLARINET study (2), 204 patients with non-functioning well and moderately differentiated pancreatic or midgut NETs (Ki-67 index up to 10%) received either Lanreotide 120mg every four weeks or placebo. Patients on Lanreotide had significantly longer progression free survival when compared to placebo (median PFS not reached v 18m, HR 0.47, 95% CI, 0.30 – 0.73, p=0.001). A subsequent open-label extension study published in 2016 found the estimated median PFS in those patients originally randomised to Lanreotide was 32.8 months (3).

In the similar, but smaller PROMID study (4), long acting Octreotide 30mg every 4 weeks resulted in significantly longer progression-free survival compared with placebo (14.3 vs 6 months, HR 0.34, 95% CI, 0.20 to 0.59, p=0.000072). This study only included well differentiated midgut NETs and included both functional and non-functional tumours.

The optimal timing of starting SSA in asymptomatic patients is controversial and uncertain. It is important to discuss the potential risks and benefits with asymptomatic patients in relation to surveillance vs upfront SSA. Current US National Comprehensive Cancer Network (5) and European Neuroendocrine Tumour Society Consensus Guidelines (6) suggest commencing upfront SSA in those patients with asymptomatic but high volume, well differentiated gasteroenteropancreatic NETs. Patients with lower volume asymptomatic disease can be counselled regarding the pros and cons of surveillance versus upfront SSA given the often slowly progressing nature of well to moderately differentiated NENs. The lack of overall survival gain with both trials does also support the potential to watch and wait for some patients.

The Australian PBS reimburses Long Acting Octreotide and Lanreotide for WHO grade 1 and 2 non-functional gastroenteropancreatic NETs under specific conditions as listed on the PBS website. The recommended starting dose as per the trials evidence when used for an anti-proliferative effect is Octeotide LAR 30mg or Lanreotide 120mg every 4 weeks.

Whilst only reported as an abstract at the time of this review, the phase II ATLANT trial (NCT02698410), investigated the effectiveness and safety of Lanreotide (120mg, every 28 days) in combination with Temozolomide (250mg/day over 5 days, every 28 days) in 40 patients with progressive well-differentiated thoracic neuroendocrine tumours (90% bronchial NET, 10% thymus). Median progression free survival was reported at 37.1 weeks (95% CI: 24.1 - 52.9). Treatment was generally well tolerated, although 2 patients experienced a severe treatment related adverse event.

The SPINET trial (NCT02683941) is a phase III trial investigating the effectiveness of Lanreotide vs placebo in lung neuroendocrine tumours, but was not yet published at the time of this review. Other evidence supporting SSAs for non gastroenteropancreatic NENs at the time of this review is based on retrospective evidence only and is not currently PBS listed for this indication.

1.3 Prevention/treatment of carcinoid crisis

Carcinoid crisis is a rare but life-threatening complication of functionally active NENs. It most commonly occurs during surgery, biopsy or anaesthesia and rarely during or shortly after peptide receptor radionuclide therapy (PRRT). Symptoms include refractory hypotension, flushing and diarrhoea.

Short acting octreotide should be readily available and prophylactic doses should be considered, particularly in those with high hepatic disease burden. Refer to Chapter 5: Surgery (Peri-operative Management) for further information on use of SSAs for peri-operative management and prevention of carcinoid crisis.

2. Targeted therapies

The decision to use targeted therapies, chemotherapy or peptide receptor radionuclide therapy (PRRT) after failure of SSA is complex and is subject to current ongoing trials. Patients should ideally be referred for discussion to a specialist NEN MDT where possible, particularly if PRRT is being considered.

NENs are highly vascular and are known to express vascular endothelial growth factor (VEGF) and its receptor (VEGFR)(7). Agents targeting the VEGF axis (e.g. sunitinib) and its downstream serine/threonine kinase mammalian target of rapamycin (mTOR) (e.g. Everolimus) have shown significant activity in published reports of randomised studies. Sunitinib and Everolimus have not been compared in any large trial in this setting and the selection of either should be based on the patients' history and side effect profile. Sunitinib and Everolimus are PBS reimbursed for the treatment of patients with well differentiated metastatic or unresectable pancreatic NENs that have either progressed on SSA or are still symptomatic despite SSA.

2.1 VEGF Inhibitors

Sunitinib is a potent inhibitor of multiple receptor kinases (VEGF, PDGFR, RET, c-Kit). In the phase III SUN 1111 trial (8), Sunitinib was compared to placebo in 171 patients with metastatic or unresectable well differentiated pancreatic NETs. When compared with placebo, Sunitinib had a significantly improved progression free survival (11.4 vs. 5.5 months; HR, 0.42; 95% CI, P < 0.001).

There was also a non-significant trend towards overall survival benefit (38.6 v 29.1 months; HR, 0.73; 95% CI, p=0.094) at a planned follow up analysis (9).

Whilst not PBS reimbursed, there have been several other smaller phase II trials investigating the effectiveness of other medications targeting the VEGF pathway in advanced well differentiated NETs. Further phase III evidence is currently the subject of ongoing clinical trials (e.g. CABINET study – NCT03375320), however some of the larger phase II trials are listed below.

Alliance A021202 randomly assigned 171 patients with progressive advanced well differentiated non pancreatic NETs to pazopanib 800mg daily or placebo (10). Whilst only available as an abstract at the time of this review, median PFS was reported as 11.6 months with pazopanib vs 8.5 months in placebo (HR 0.53, 1-sided 90% upper confidence limit, p = 0.0005). Overall survival was similar but significant cross-over was reported.

In a smaller phase II study, 52 patients with metastatic or locally advanced grade 1-2 NETs were assigned Pazopanib 800mg once daily and long acting Octreotide (11). 32 patients had pancreatic NETs with the remaining 20 having small bowel NETs. In the patients with pancreatic NETs, 21% had an objective response. No patients with small bowel NETs had an objective response.

Another similar phase II study investigated Cabozantinib 60mg daily in 41 patients with well differentiated advanced small bowel NETs and 20 patients with well differentiated pancreatic NETs (12). Whilst only available as an abstract at the time of this review, the authors reported a response rate of 15% in those with pancreatic NETs with a median PFS of 21.8 months. Response rates for small bowel NETs were also 15% with a median PFS of 31.4 months.

Whilst also only available as an abstract, a promising phase II trial of lenvatinib in 110 patients reported response rates of 42% for patients with advanced pancreatic NETs and 16.3% in those with advanced small bowel NETs (13). Median PFS was reported as 29.2 months and 15.4 months respectively.

2.2 mTOR Inhibitors

Everolimus is a potent inhibitor of the mammalian target of rapamycin (mTOR), a signalling pathway implicated in neuroendocrine tumourigenesis (14)(15). The efficacy and safety of Everolimus has been investigated in four main trials – the RADIANT trials.

The first of which was the RADIANT-1 phase II trial which investigated Everolimus alone vs Everolimus + Octreotide in 160 patients with advanced pancreatic NETs who had progressed on cytotoxic chemotherapy (16). The median PFS was 9.7 months (95% CI, 8.3 to 13.3 month) in the Everolimus group and 16.7 months (95% CI, 11.1 months to NA) in the combination group.

RADIANT-2 was a subsequent larger phase III randomised control trial that compared Placebo plus Octreotide to Everolimus + Octreotide in 429 patients who had low or intermediate grade advanced NET associated with carcinoid syndrome that had progressed in the prior 12 months (17). Around 50% of patients had the small intestine as the origin of their NET with only around 5% pancreatic. The median PFS was 11.3m in the placebo group and 16.4 months in combination group (HR 0.77 – not significant, 95% CI, 0.59 – 1.00, p=0.026). Whilst not statistically significant, the pre-specified cutoff for statistical significance was close at p=0.0246.

RADIANT-3 was a large phase III randomised control trial of 410 patients that compared placebo to Everolimus in 410 patients with low to intermediate grade advanced pancreatic NETs who had progressed in the prior 12 months (18). The median PFS was 11m in the Everolimus group and 4.6m in placebo (HR 0.35; 95% CI 0.27 - 0.45; p<0.001). Overall survival did not differ between groups, however 75% of patients in the placebo arm crossed over to Everolimus on progression.

Finally, RADIANT-4 was a phase III trial that also compared Everolimus to placebo but in 312 patients with well differentiated, non-functional advanced NETs of lung or GI tract origin (not pancreatic) that had progressed in the prior 12 months (19). The median PFS was 11m in the Everolimus group and 3.9m in the placebo group (HR 0.48, 95% CI 0.35 – 0.67, p=<0.0001).

The above results support the use of Everolimus or Sunitinib in metastatic well to moderately differentiated advanced pancreatic NETs that have progressed or are still symptomatic despite SSA. Whilst evidence in the RADIANT 2 and ALLIANCE A021202 trials also suggests benefit of Everolimus and Pazopanib in non-pancreatic NETs, this indication is currently not PBS funded in Australia.

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