Chapter 10: Peptide Receptor Radionuclide Therapy

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Practice Points

1. Peptide receptor radionuclide therapy (PRRT) is a molecularly targeted radiation therapy involving the systemic administration of a radiolabelled peptide which targets somatostatin receptors (SSR) overexpressed on neuroendocrine neoplasms (NENs).

2. PRRT can be considered in patients whose NENs express somatostatin receptors as demonstrated by modern somatostatin receptor imaging using whole body ^{68}Ga DOTA peptide PET/CT scans.

3. Final patient selection for PRRT should be made in the context of a neuroendocrine tumour multidisciplinary team (MDT) meeting in centres with experience in the delivery of PRRT.

4. The currently available radionuclide of choice is ^{177}Lutetium- (^{177}Lu) coupled to a somatostatin analogue DOTA-octreotate (DOTATATE), ^{177}Lu- DOTATATE (LuTate). Standard protocols usually deliver 4 cycles at 8 weeks intervals. Retreatment can be offered upon disease progression in appropriately selected cases, following MDT discussion. A range of other radionuclides and peptides, both beta and alpha emitters, are being evaluated for safety and efficacy.

5. In patients with WHO grade 1-2 midgut NENs, randomized trial evidence from the NETTER-1 study, supports the use of PRRT as second-line treatment following progression on standard long-acting somatostatin analogues to improve progression free survival and patient quality of life. Further studies are ongoing to evaluate the place of PRRT in patients with NENs originating from other primary sites or with higher grade.

6. More prospective data is needed to evaluate the overall place of chemotherapy [capecitabine alone or Capecitabine/Temazolomide (CAPTEM)] in combination with PRRT as routine therapy in patients with GEP NENs. On the limited evidence available, chemotherapy can be considered with PRRT for selected patients with pancreatic NENs (with CAPTEM), and possibly midgut NENs, with high tumour burden or poor prognostic factors where tumour response is important for patient benefit.

Basic overview of PRRT

Peptide receptor radionuclide therapy (PRRT) is a molecularly targeted radiation therapy involving the systemic administration of a radiolabelled peptide which targets somatostatin receptors (SSR) overexpressed on neuroendocrine neoplasms (NENs). PRRT was guided by largely retrospective data for many years (1), until Strosberg et al published the results of the first randomised, controlled trial (RCT), NETTER-1 in 2017 (2) in which 4 cycles of 7.4 GBq ^{177}Lu- DOTA-octreotate (^{177}Lu-DOTATATE) demonstrated a clinically and statistically significant improvement in PFS as a primary endpoint (HR: 0.18, $p < 0.0001$) as well as a clinically meaningful trend towards improvement in median OS of 11.7 months over high dose Somatostatin Analogue (SSA) therapy alone for midgut neuroendocrine tumours. No new safety signals emerged during the 5-year long-term follow-up (3).

In addition to this RCT data for small bowel NENs, the benefit of PRRT is known to extend to a broad range of SSR-expressing NENs of different origin and grading within the advanced metastatic setting. In January 2018, ^{177}Lu-DOTATATE (Lutathera™) was granted approval for gastroenteropancreatic neuroendocrine tumours (GEP-NETs) by the US Food and Drug Administration (FDA). This approval has seen greater acceptance and more widespread use of PRRT internationally, although at the time of writing, therapy with ^{177}Lu-DOTATATE is not included in the Australian Register of Therapeutic Goods (ARTG) and its use requires individual approval via Category A Special Access Scheme (SAS) through the Therapeutic Goods Administration (TGA).

When the Clinical Oncology Society of Australia (COSA) guidelines for the management of neuroendocrine tumours were originally published in 2010, no other international guidelines formally included PRRT in the treatment algorithms. However, over the ensuing decade, PRRT has gained greater acceptance with progressive integration into therapeutic guidelines. These include the joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours 2013 (4), ENETS Consensus Guidelines 2017 (5), ESMO 2020 (6), NANETS/SNMMI Consensus Statement 2020 (7), EANM Focus 3 Consensus (2021) (8), National Comprehensive Cancer Network (NCCN) Guidelines Version 2.2021 (9) and Version 1.2022 (10).

The current radionuclide(s) of choice is the beta emitting radionuclide ^{177}Lutetium- (^{177}Lu) coupled to a somatostatin analogue DOTA-octreotate (DOTATATE), ^{177}Lu-DOTATATE. ^{177}Lu-DOTATOC is being used in Phase III clinical trials. The first generation radionuclide ^{111}Indium-Octreotide or octreotate is now rarely used, and ^{90}Yttrium is usually reserved for use in certain centres for selected patients especially for larger lesions. Preliminary work has suggested a potential role for PRRT with targeted alpha therapy using ^{225}Ac-DOTATATE in patients who are refractory to other treatments, but this treatment is still regarded as experimental and further prospective data is warranted (11).

A key factor leading to successful treatment is timely patient selection based on biological tumour properties that are evaluated with functional imaging using PET/CT to evaluate somatostatin receptor expression and FDG uptake. Individualised patient selection is integral in ensuring sufficient expression of the target SSTR2 for therapeutic benefit and reflects the advances in personalised medicine (12).

The role of dosimetry, the addition of radiosensitising chemotherapy or combination treatments and the role of targeted alpha therapy remain under investigation and are discussed briefly in following sections.

Patient selection for PRRT

With the marked heterogeneity of NENs, there remain many unanswered questions regarding optimal patient selection and sequencing of treatment. The 2017 European Neuroendocrine Tumour Society (5) and 2020 NANETs/SNMMI (7) guidelines and consensus statements, respectively, have each summarised the literature to date and are referenced for completeness.

Baseline structural imaging with ultrasound, CT or MRI will evaluate the burden of disease, site and volume of metastases and also assist in response assessment using the RECIST 1.1 criteria. Functional imaging using ^{68}Ga DOTA peptide PET/CT will demonstrate eligibility by ensuring the therapeutic target, somatostatin receptor (SSTR) is present for all lesions.

Imaging with whole body ^{68}Ga DOTA peptide PET/CT is the preferred imaging modality as outlined in Medicare Benefits Schedule (Item 61647). Higher grade tumours require further work-up with whole body ^{18F}FDG PET/CT to confirm eligibility for PRRT; all lesions must have high SSR expression to be targeted by PRRT. (Link to Chapter 4: Medical Imaging)

The next consideration is the site of primary tumour, with NETTER-1 providing evidence of therapeutic benefit for midgut NENs. To date, no Phase III RCTs of PRRT have been performed in patients with NENs arising from other primary locations, and further prospective trials are warranted, with some already underway. The AGITG CONTROL NET study is the only Phase II study with randomised data in pNETs. However, there exists a large pool of data, mostly retrospective, supporting the effectiveness of PRRT for SSR expressing disease from other primary sites, including pancreatic NETs and bronchial NENs. A pooled analysis of eight studies (2 prospective, 6 retrospective) reported positive outcomes of PRRT in pancreatic NETs (13).

Further eligibility criteria for PRRT, comprehensively described in both Hicks and Hope (5, 7) include adequate hepatic, renal and haematological reserve demonstrated in biochemical and haematological parameters. However, real world patient selection for treatment may require decision making for treatment where patients may not have been eligible based on traditional clinical trial organ function cut-offs.

Renal insufficiency

Based on available data, SNMMI/NANETs do not consider a GFR < 50 ml/min to be an absolute contraindication to ^{177}Lu-DOTATATE use. For patients with severe baseline renal dysfunction defined as GFR < 30 ml/min, ^{177}Lu-DOTATATE should be used only in exceptional circumstances. Of note, hydronephrosis represents a particular concern as it impairs renal excretion and clearance, and potentially increasing radiation dose. As much as possible, hydronephrosis should be corrected before initiation of ^{177}Lu-DOTATATE treatment. Patients on dialysis may be treated with ^{177}Lu-DOTATATE, but as with other radio-pharmaceutical therapies, this should be done very carefully, with consideration for dose reduction and dosimetry.

Evidence summary and published guidelines

We have listed below a consensus regarding PRRT based on the primary site of NEN, noting that there is no single recognised international guideline. (7)

Midgut NEN

^{177}Lu-DOTATATE should be considered in SSR-positive patients at time of progression after treatment with first line somatostatin analogue therapy based on data from the Phase III NETTER-1 Trial.

The NETTER-1 trial, a double-blind, randomized, controlled study evaluated ^{177}Lu-DOTATATE versus high-dose octreotide, enrolled grade 1 or 2 midgut NET patients with metastatic or locally advanced progressive tumours during treatment with standard long-acting octreotide.

The NETTER-1 trial demonstrated an improvement of progression-free survival (PFS) and Global health related Quality of Life (HRQOL) for ^{177}Lu-DOTATATE compared with the control arm.

Objective response rate with ^{177}Lu-DOTATATE was 18%, versus 3% with high-dose octreotide.

Pancreatic NEN

FDA included pancreatic NET (pNET) within the indication for ^{177}Lu-DOTATATE, and PRRT should be considered for treatment in patients with progressive pNETs on standard therapies. However, the optimal timing of PRRT in the pNET treatment algorithm is not known.

Outside of the NETTER-1 trial, there are 2 prospective studies evaluating single agent PRRT in pNETs, both single arm studies. The first is the IEO phase 1–2 trial, which included 14 pNET patients and reported an overall response rate of 57% (8/14) (14) and the second is a study of 60 pNET patients with an overall response rate of 30% (18/60) (15).

Bronchial NEN

PRRT could be considered as a potential therapeutic option for patients with SSTR-positive lung NEN, as there is increasing data suggesting that it is active and safe, associated with high disease control rate, with encouraging PFS and OS (16). Further prospective studies comparing PRRT to other systemic options are warranted.

Tumours of unknown primary

Decisions to treat with PRRT in unknown primaries should mirror those in patients with GEP NENs and ^{177}Lu-DOTATATE therapy should be considered in patients who progress despite treatment with first-line somatostatin analogue therapy.

Paraganglioma/Pheochromocytoma

These tumours are complex, heterogenous with different molecular imaging phenotype and targets. Targeted radionuclide therapies using I-131 MIBG and PRRT with ^{177}Lu-DOTATATE represent therapeutic options in the management of metastatic or inoperable pheochromocytoma and/or paraganglioma (PPGL) but clinical decision making remains challenging in the absence of randomised controlled trials in this area.

A recent international multidisciplinary expert consensus supported a personalised approach considering imaging phenotype, radionuclide with the highest uptake, whilst balancing toxicity and risk factors (17). Sequencing or combination therapy could also be considered. There is increasing data to suggest that PRRT is effective for functional disease, with more favourable radiation safety profile than I-131 MIBG. However, further multicentre prospective comparative studies are needed.

High grade disease

^{177}Lu-DOTATATE has been studied almost exclusively in patients with low or intermediate-grade neuroendocrine neoplasms (NENs). There is increasing data to support the benefit of ^{177}Lu-DOTATATE in patients with well-differentiated grade 3 neuroendocrine tumours (18-20). Despite the absence of RCTs, PRRT can still be considered as part of multi-modality treatment following discussion at MDT.

Mesenteric and Peritoneal Disease

In certain clinical circumstances, we recommend caution before consideration of ^{177}Lu-DOTATATE. Mesenteric tumours are often characterized by substantial surrounding desmoplasia. There are theoretic concerns that radiation may exacerbate the desmoplastic process, thus leading to acute

worsening of symptoms. Similar theoretic concerns pertain to patients with extensive peritoneal carcinomatosis in whom radiation may lead to bowel obstruction. Decision making in these circumstances should be made in the context of an MDT where *all* options are considered, including surgery.

Referral pathway and practicalities of PRRT

Patients being considered for PRRT should be referred to a multidisciplinary tumour board discussion. The management of patients with NENs is complex, requiring a multidisciplinary team approach in both the clinic and tumour board setting. Such an approach leads to improved outcomes and is considered the standard of care, especially for complex tumours (21).

The principal indications for MDT are to review imaging (anatomical and functional), pathology, clinical scenario, to discuss patient eligibility for PRRT and discuss therapeutic selection including trials in the context of disease and patient factors.

The pathway to PRRT for the majority of patients is via local or hospital based MDTs with referral to centres providing PRRT. In the case of regional, rural and remote patients, access is facilitated by telehealth and a quaternary institution style referral.

What are the benefits of PRRT?

To address this question, we need to look for RCTs that compare peptide receptor radionuclide therapy (PRRT) to other therapies. The only published Phase III RCT to date comparing PRRT to other therapies is the NETTER-1 study (2). The NETTER-1 study was designed to determine if PPRT with lutetium-177 (^{177}Lu)–Dotatate (Lutathera®) was more effective than high-dose long-acting octreotide (LAR) 60 mg in patients with advanced, progressive, somatostatin-receptor– positive midgut neuroendocrine tumours. This international, multicentre trial enrolled 229 patients who demonstrated disease progression on CT or MRI any time for at least 12 weeks on octreotide LAR 20 – 30 mg every 3-4 weeks over a period up to 3 years prior. The intervention arm (^{177}Lu-Dotatate group) involved 7.4 GBq of ^{177}Lu-Dotatate infused intravenously over four infusions every 8 weeks, in addition to best supportive care including the addition of octreotide LAR 30 mg approximately 24 hours after each infusion of ^{177}Lu-Dotatate and then monthly after completion of all four treatments. All patients received renal protection with an intravenous amino acid solution.

The NETTER-1 study did not evaluate PRRT monotherapy, however the continued administration of LAR with PRRT could be argued to reflect routine practice in preventing carcinoid symptom flare from its withdrawal. The primary efficacy endpoint was progression-free survival (PFS) by blinded independent central CT review with standard secondary endpoints including objective response rate (ORR by RECIST criteria), overall survival, quality of life (QoL) and safety. In the initial publication of the study, PFS favoured ^{177}Lu-Dotatate (median not reached, 8.4 months in the control group), resulting in a hazard ratio of 0.21 (95% Confidence interval (CI) 0.13-0.33; $p < 0.001$). Benefit was observed across all relevant patient subgroups. ORR favoured ^{177}Lu-Dotatate over control, 18% vs 3%, $p < 0.001$ (2). There was more nausea, vomiting, fatigue, reduced appetite, headache, alopecia and cytopenias with ^{177}Lu-Dotatate treatment, but only 5% of patients in the ^{177}Lu-Dotatate

withdrew from study treatment due to adverse events (2). Eight patients required dose reduction and 77% completed all 4 treatments.

In regard to QoL, this was evaluated using the European Organisation for Research and Treatment of Cancer quality-of-life questionnaires QLQ C-30 and G.I.NET-21 (22). Time to QoL deterioration (TTD) was defined as the time from random assignment to the first QoL deterioration ≥ 10 points for each patient in the corresponding domain scale. TTD was longer in the ^{177}Lu-Dotatate arm versus the control arm for global health status (HR 0.406), physical functioning (HR 0.518), role functioning (HR 0.580), fatigue (HR 0.621), pain (HR 0.566), diarrhoea (HR 0.473), disease-related worries (HR 0.572), and body image (HR 0.425) (22). Improvement in QOL has been reported in several prior PRRT studies (23-26).

A small proportion of pancreatic NEN can secrete specific hormones causing distinct functional syndromes, and the most typical are gastrinoma, insulinoma, and glucagonoma. Despite reports mainly generated from retrospective institutional series, there is increasing data and experience supporting the effectiveness of PRRT in patients with significant functional syndromes and in achieving oncologic control from pancreatic NEN (27-31). Further multicentre PRRT trials are needed to confirm the utility of PRRT in these rare subgroups.

Ongoing RCTs evaluating the effectiveness of PRRT versus other therapies

COMPETE trial (NCT03049189): Randomized Phase III study of ^{177}Lu-Edotreotide compared to targeted molecular therapy with Everolimus in patients with inoperable, progressive, somatostatin receptor-positive (SSTR+), neuroendocrine tumours of gastroenteric or pancreatic origin (GEP NET).

NETTER-2 trial (NCT03972488): Randomized Phase III study evaluating Lutathera® in combination with long-acting octreotide in GEP NET patients with high proliferation rate tumours (G2 and G3), when given as a first line treatment compared to treatment with high dose (60 mg) long-acting octreotide. Somatostatin analogue (SSA) naive patients are eligible, as well as patients previously treated with SSAs in the absence of progression.

COMPOSE trial (NCT04919226): Lutetium 177Lu-Edotreotide versus Best Standard of Care (FOLFOX, CAPTEM or Everolimus) in Well-differentiated Aggressive Grade-2 and Grade-3 GastroEnteroPancreatic NeuroEndocrine Tumours (GEP NETs).

Additional trials can be reviewed on clinicaltrials.gov

Is PRRT with radio-sensitizing chemotherapy superior to PRRT alone?

There have only been two reported RCTs evaluating the use of chemotherapy concurrent with PRRT (32, 33). The rationale of combining drug therapy with PRRT is based on the principle of radiosensitization (34), initially used to describe agents that enhance the ability of radiation to kill tumour cells when the agent has no single agent activity on the tumour, although most drugs used have had anti-tumour activity themselves.

In the case of PRRT in NENs, the first agent reported in combination with PRRT was the thymidylate synthetase inhibitor capecitabine. In a study led by the Rotterdam group in the Netherlands, PRRT with ^{177}LuDotatate 7.4 GBq Q 8 weeks x 4 and capecitabine (1650 mg/m2/day bid days 1-14 Q 8

weekly) was compared with PRRT alone in metastatic or inoperable GEPNET patients (33). This study was reported only as a meeting abstract and not in full publication. Sixty-one patients were enrolled in the PRRT control arm and 50 to the investigational arm respectively from 2006-2013. Median PFS was 36.2 months (95% CI 29.1-43.4) (control) and median OS 64.6 months (95% CI 39.7-89.4) (PRRT group). In the capecitabine/PRRT group, PFS was 47.7 months (95% CI 33.1-62.4, p=0.38) and median OS 75.8 months (95% CI 54.3-97.2); (p=0.50). Grade III-IV haematological toxicity was observed in 16.4% and 22.0% (p=0.48) respectively.

The next reported RCT evaluated the chemotherapy regimen CAPTEM (capecitabine and temozolomide) combined with ^{177}LuDotatate (LuTate). This Phase II study, led by the Australasian Gastro-Intestinal Trials Group (AGITG) aimed to evaluate the activity of LuTate/CAPTEM combined, relative to control in a parallel group design in patients with midgut NETs (mNETS, LuTate control) and pancreatic NETs (pNETS), CAPTEM control) (32). This was a non-comparative randomised open label phase II trial with 2:1 randomisation to PRRT/CAPTEM (experimental arm) vs PRRT (mNETs control) and CAPTEM (pNETS control). PRRT/CAPTEM was administered at a dose of 7.8GBq LuTate 8 weekly (wkly) x 4, with b.i.d. oral CAP 750mg/m^2 Days 1-14 & oral TEM 75mg/m^2 Days 10-14, 8 wkly x 4. In the midgut NET arm, the control group received PRRT alone 8 wkly x 4; in the pancreas NET arm the control group received oral CAPTEM 4-wkly x 6. The primary endpoint of the study was PFS. Secondary endpoints included ORR, toxicity, and quality of life, resource utilisation with an exploratory tertiary correlative study.

Seventy-five patients were enrolled from 4 Australian PRRT centres (from Dec 2015 to Nov 2018): mNETs 33 received PRRT/CAPTEM and 14 received PRRT; pNETS 19 received PRRT/CAPTEM and 9 received CAPTEM. In the midgut NET group, the final target 15mo PFS rate was 90% (95% CI: 73-97%) in patients receiving PRRT/CAPTEM vs 92% (95% CI: 57-99%) in patients receiving PRRT alone; ORR in the midgut NET group was 34% vs 23% for PRRT/CAPTEM v PRRT respectively. Most of the grade 3/4 toxicity was asymptomatic haematologic toxicity, more frequent in the combination arm. Only one patient failed to complete therapy (in the PRRT/CAPTEM arm). In the pancreas NET arm the target 12 mo PFS rate was 83% (95% CI: 57-94%) in the group receiving PRRT/CAPTEM vs 89% (95% CI: 43-98%) in the control group receiving CAPTEM alone; ORR was 72% vs 33% for PRRT/CAPTEM vs CAPTEM respectively. At final analysis [median follow up 57 months (pNETs) and 60 months (mNETs)], there was a strong trend in PFS in the pNET arm (PFS HR 0.15-1.12; p = 0.08), but no difference in the mNET arm.

Regarding treatment related AEs, 5/18 PRRT/CAPTEM patients had at least one Grade 3 event (28%) vs 3/9 (33%) CAPTEM alone; and 3/18 pts at least one Grade 4 event (17%) vs 1/9 (11%) respectively, mostly haematologic. After long term follow up, late grade 3/4 haematologic AEs were as follows: mNETS: 2/32 (6%) PRRT/CAPTEM patients and 4/13 (31%) PRRT patients. Events included myelodysplastic syndrome (at 40 months), leukaemia (at 60 months), pancytopenia (at 50 months), anaemia (at 32 months), thrombocytopenia (at 7 months). No late haematologic Grade 3/4 AEs were reported in the pNETS cohort. No late renal toxicity was identified in all study arms.

The CONTROL NET study met its primary endpoint for CAPTEM/PRRT combined in the pNET population of >= 75% PFS at 12 months and in the mNET population of >= 80% PFS at 15 months, with numerically greater ORR with combination therapy in both arms (2-fold increase in pNET arm), at the expense of modest toxicity, mainly haematologic. Long-term follow up confirmed durable activity but no significant difference in PFS in the mNET study arms, although a strong PFS trend in favour of CAPTEM/PRRT over CAPTEM was observed in the pNET arm, without long-term toxicity.

Evidence summary

PRRT with ^{177}Lu-Dotatate and concomitant capecitabine appears to be safe and is associated with a trend toward longer progression-free survival, however this single RCT evaluating this combination was underpowered to draw conclusions on the overall effectiveness of this combination. PRRT/CAPTEM combined appears to be safe and associated with a higher response rate than PRRT alone (mNETS) and CAPTEM alone (pNETS), but with greater acute haematologic toxicity. The magnitude of benefit was greatest in the pNET population where no late haematologic toxicities were observed. A larger comparative Phase III RCT in pNETs is required to determine the overall benefit of this combination.

Short-term toxicity of PRRT

PRRT is generally well tolerated by patients. Nausea is common during the renoprotective amino acid and radiopeptide administrations, but routine pre-medication with anti-emetic drugs and slow infusion of the radiopeptide (over 15-20 minutes) results in only mild symptoms in most patients. Some fatigue during the week following treatment is common, but is also rarely severe. Temporary, mild (G1) hair loss has been reported in 60% of patients after ^{177}Lu-DOTATATE therapy (5).

Patients with abdominal pain, nausea or significant hormone-secretory symptoms, may experience a temporary flare for a few days following PRRT and should be provided adequate pain relief and anti-emetic medications.

In patients with severe carcinoid syndrome, short-acting octreotide should be available to manage a carcinoid crisis, which can occasionally develop soon after PRRT, although even highly symptomatic patients generally tolerate their treatment well. Patients with poorly controlled carcinoid symptoms may require inpatient admission for monitoring and acute care, with multidisiciplinary team and potentially intensive care support. Other hormonal effects (e.g. hyperinsulinism) should be managed in consultation with an endocrinologist.

While mild myelotoxicity is typically seen post PRRT, severe bone marrow toxicity (Grade 3-4) is uncommon and is most often seen in heavily pre-treated patients or those having concurrent chemotherapy (32). Routine monitoring of patients' blood counts is performed and each treatment should be deferred until bone marrow function is 'adequate'. There is no agreed definition of adequate bone marrow function in this context and the risks and benefits of continuing therapy should be weighed for each patient, preferably in a multidisciplinary setting.

Long-term lymphopaenia, with predominant B-cell depeletion, is common following PRRT but does not usually result in an increased risk of infection.

Recent reviews do not suggest that there is any clear evidence that PRRT places patients at significantly greater risk of developing more severe infection-related complications, including COVID-19 (35).

Long-term toxicity of PRRT

Side effects of greatest long-term concern of ^{177}Lu-DOTATATE therapy include potential renal and marrow toxicity. ^{90}Y is considered more nephrotoxic due to the longer range of its beta particle. A recent large series of 807 patients found that treatment with ^{90}Y or combined ^{90}Y + ^{177}Lu was more likely to result in nephrotoxicity than treatment with ^{177}Lu alone, but severe renal complications were uncommon (1.5%) (36). Long-term follow-up by other groups have also demonstrated low rates of nephrotoxicity from ^{177}Lu when used with amino acids (5). The NETTER-1 study included patients with GFR ≥ 50 ml/min prior to treatment and some patients with baseline GFR between 30-50 ml/min also received PRRT as part of this study. No significant nephrotoxicity was observed during follow-up in patients with even moderate renal impairment. Even among patients with baseline renal impairment, acute deterioration in renal function following PRRT is more likely to reflect changes in hydration (i.e. pre-renal causes) than treatment-related toxicity. Identification and management of functional urinary tract obstruction should also be considered prior to commencing PRRT.

Subacute grade 3 or 4 haematological toxicities have been reported to occur in up to 11% of patients (37). The development of a haematopoietic neoplasm after PRRT is categorised as therapy-related myeloid neoplasm (t-MN) (2016 WHO classification) (38), comprising patients developing myelodysplasia (MDS) or acute myeloid leukaemia (AML). The incidence for t-MN ranges from 1 to 5.4% (36, 37, 39, 40), but underlying mechanisms remain poorly understood. Bodei et al. reported an incidence of MDS/AML of 3.45% in the largest yet-reported cohort of 807 patients. A recent systematic review of 28 studies reported variable incidences between studies with mean (standard deviation) t-MN incidence after PRRT of 2.61% (4.38%) (41).

Median time of developing t-MN after first PRRT treatment was variable between studies, but most were diagnosed after 1 year from PRRT (range 4-125 months) (41). Potential variables associated with these events in one study were duration of PRRT and platelet toxicity grade during treatment (36), but overall data is limited. No other definite patient or treatment associated factors have consistently been identified across studies, raising the possibility of pre-existing biological or genetic susceptibility as potential contributing factors, which would require further prospective investigation. In the NETTER-1 study, Grade 3 or 4 neutropenia, thrombocytopenia and lymphopenia occurred in 1, 2 and 9% of patients in the PRRT arm versus none in controls. Two cases (2%) of MDS were attributed to PRRT, and no new cases of MDS or AML were diagnosed during long-term follow-up (3).

In the CONTROL NET study, median mNET follow-up was 60.3 months; pNETs mFU 57.5 months. Late grade 3/4 haematologic AEs were seen in midgut NET patients -2/32 (6%) PRRT/CAPTEM patients and 4/13 (31%) PRRT patients. Events included myelodysplastic syndrome (at 40 months), leukaemia (60 months), pancytopenia (50 months), anaemia (32 months), thrombocytopenia (7 months). No late haematologic grade 3/4 AEs were reported in the pNETS cohort. No late renal toxicity was identified in all study arms (32).

While t-MN appear relatively uncommon, this remains of clinical importance. Interestingly, t-MN incidence after PRRT in NEN appears to be higher compared to other solid tumours treated with chemotherapy and/or radiotherapy. A recent large population-based study of more than 700,000 patients with solid tumours treated with chemotherapy, identified 1,619 cases of t-MN (42). Specifically, in breast cancer, after initial therapy the cumulative 10-year t-MN incidence is 0.5%

(43). These observations raise the interesting issue whether there are intrinsic patient factors associated with NEN, PRRT and the evolution of t-MN.

Genetics remain an important prognostic factor and patients with t-MN often have notable unfavourable complex cytogenetic aberrations; for example a high frequency of tumour protein 53 (TP53) pathway mutations (44, 45). A recent retrospective analysis showed that the clonal abnormalities found in PRRT or PRCRT-related t-MN is complex and similar to what is seen in other t-MN secondary to conventional radiation and alkylating agents, together with the recognised consequences of overall poor survival and limited response to available t-MN therapies (40, 41). However, most patients had favourable oncologic responses from PRRT and subsequent long-term stability prior to t-MN diagnosis.

Recently, Scarpa et al., demonstrated that pancreatic NETs contain a larger-than-expected proportion of germline mutations, including DNA repair genes (46). These overall observations raised an interesting hypothesis of pre-existing biological, genetic susceptibility or germ-line mutations as potential contributing factors to development of t-MN. Therefore, well-structured prospective studies are needed to explore the risk factors predicting t-MN development after PRRT including both clinical and biomarker factors, and to define a mechanism of action for this relatively uncommon but clinically important complication.

Future Directions and Emerging Therapies

Given the importance of somatostatin receptors (SSRs) in NEN biology and the impressive outcome observed with ^{177}Lu-DOTATATE, novel PRRT strategies encompassing the use of radiolabelled SSR antagonists theranostic pair and alpha-emitting radiolabelled somatostatin analogues (SSAs) are being actively investigated.

The best evaluated novel radiolabelled SSR antagonists theranostic pair is [^{68}Ga]-OPS202, with its therapeutic partner [^{177}Lu]-OPS201. The use of radiolabelled SSTR antagonists rather than agonists (ie -TATE and -TOC) has the potential to improve SSTR receptor PET/CT imaging and deliver a higher tumour dose per injected activity, because antagonists may recognise a higher number of SSTR binding sites (47-51).

Alpha-emitting radiolabelled somatostatin analogues (SSAs) currently under investigation include ^{225}Ac-DOTATATE, ^{213}Bi-DOTATOC and ^{212}Pb-octreotate. ^{225}Ac-DOTATATE is currently the best evaluated alpha-emitter, and has been studied in a well-designed prospective case series with a well-defined patient cohort which showed that 67.5% of its patients achieved partial remission following 2 cycles of ^{225}Ac-DOTATATE of 100kBq/kg without any patients experiencing progressive disease (52, 53).

The future place of these new therapies/technologies in the treatment algorithm for NENs will be defined by ongoing prospective studies.

Future directions also include potential new developments of novel combination treatments, new radionuclides, theranostic pair, new NEN targets, and strategies towards a more personalised approach.

Dosimetry Considerations

There is no broad consensus on the optimal way to approach PRRT dosimetry (54). Dosimetry may be used to administer the maximum cumulative activity which does not exceed toxic doses to key target organs (bone marrow, kidneys), or to estimate the absorbed dose to key target lesions, with a view to achieving tumoricidal doses.

Numerous dosimetry protocols have been published using a variety of methods, including single vs multiple time points, 2D and 3D acquisitions and a range of analytical techniques and software (55). While no single method has been recommended to date, there is an increasing trend to perform lesional dosimetry using hybrid 2D/3D analytical techniques at multiple time points. Single time point analysis at 24 or 96 hrs post-administration provides less accurate, but broadly acceptable, dose estimates and may be more relevant in Australia, where patients sometimes travel long distances to receive treatment.

All dosimetry should be performed by an appropriately trained medical physicist.

Most centres currently administer a fixed activity of ^{177}Lu-octreotate, typically 7.4 GBq (200 mCi) per treatment cycle. This activity was originally chosen on the basis of dosimetry studies to deliver a cumulative absorbed bone marrow dose $\leq$ 2 Gy over four treatment cycles (56).

This activity also typically results in cumulative renal doses slightly below the safe upper limit. Lower activities (e.g. 3.7-5.5 GBq) may be prescribed for patients with reduced renal or bone marrow function, or in those receiving intra-arterial administration of radionuclide. Dosimetry can also permit safe escalation of administered activity in some patients, sometimes by as much as 50%. There is no data yet which shows improved outcomes following individualised dosimetry.

Following PRRT, patients can be discharged from hospital when their emission rate has declined to 25 μSv/hr, typically within 4 hrs of administration. Patients, and their household members, should be given specific advice regarding radiation safety precautions at home, and supplied with a document which details their therapy and the steps required if they should present for medical care in the week following PRRT.

Prospective studies have shown that there is no significant environmental safety risk from patients who have received PRRT (57).

References

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