Peptide receptor radionuclide therapy

Indications – Somatostatin receptor positive tumours (esp. SSTR type-2):

Predominantly Gastroenteropancreatic neuroendocrine tumours or GEP NETs (e.g. carcinoid; islet cell tumours etc.)

Other tumours that express SSTR:

- Pituitary adenoma
- Meningioma
- APUDoma (e.g. malignant pheochromocytoma; paraganglioma; SSTR positive neuroblastoma)
- Small cell lung cancer
- Medullary thyroid cancer
- Parathyroid tumours
- Certain breast cancers
- Malignant lymphoma (SSTR positive)

Purpose of SSRT imaging prior to therapy:

- Assists us in patient selection
- Assists us in tumour localization
- Used for staging/re-staging
- Useful in Response prediction
- Useful Radiotoxicity prediction
- Monitoring response to various treatment options

Tracer options (SSRT affinities in brackets):

- ^{111}In-DTPA-Octreotide (2; less for 1-5)
- ^{99m}Tc-Tektrotyd
- R-DOTA-Peptides:
  - TOC (2; more than Octreotide)
  - TATE (2; most)
  - NOC (2,3,5)
  - BOC (2,3,5)
  - LAN (3,5; less for 2)
  - PAN (1-5)

We will use predominantly ^{177}Lu-DOTATOC since this is easily obtainable in South Africa. All of DOTA-labelled pharmaceuticals have similar effect however.

Inclusion criteria:

- Inoperable tumours
- Progressive GEP NETs (non-indolent) i.e. growing in size; raised tumour markers; increased symptoms; significant weight loss
- Limited disease with cure potential
- Extensive tumour load
- Patients with hepatomegaly
- Tumour uptake of SSTR tracer > liver – requires a "distribution & dosimetry" study e.g. ^{111}In-DTPA-Octreotide; ^{68}Ga-DOTA-Peptide; ^{86}Y-DOTA Peptide)
- Volumetric analysis for dosimetry via CT or MRI scans

Exclusion criteria:

- Pregnancy
- Breastfeeding
- Chemotherapy < 6 weeks prior
- Long-acting SST-analogues taken weeks prior to scheduled therapy
- Liver insufficiency i.e. bilirubin ≥ 3x upper limit of normal; s-Albumin < 30g/L
- Severe cardiac impairment
- Renal impairment (i.e. GFR < 40 ml/min; S-Cr > 150 µmol/L)
- Haematological dysfunction (WCC < 2-3.5 x 10^9/L; Platelets < 100 x 10^9/L; Hb < 5mmol/L)
- Urinary incontinence
- Life expectancy < 3-6 months
- Karnofsy score < 50%; ECOG score ≥ 4

Side effects – the following may occur:

- Nausea & vomiting (esp. due to pre-therapy amino acid administration)
- Pain at tumour sites
- Mild hair loss (^{177}Lu-DOTA-Peptides)
- Transient myelosuppression (especially after chemotherapy or external beam radiation therapy)
- Nephropathy (acute and delayed) – progressive; depends on total absorbed dose, dose volume, fractionation rate; history of diabetes mellitus or hypertension and prior EBRT
- Hepatotoxicity (especially large hepatic tumour burden; decreased reserve; radiation absorbed dose to hepatic tumour)

Work-up:

- Informed consent – will include:
  - Verbal and written consent
  - Side-effects
  - Personal radiation hygiene
  - Personal radiation safety e.g. travel
  - Care-taker consent for possible exposure > 1 mSv
  - Distance, time and shielding instruction for care-taker
  - Radiation monitoring (dosimeter for external and urine collection for internal)
- Baseline tumour markers (especially Chromogranin A) will be taken
- Standard blood tests will be performed – LFT; U&E; Haematology
- MAG-3 dynamic renogram will be performed for follow-up purposes (to assess changes in renal function)
- The patient will require a distribution scan to assess eligibility for therapy & other scans
- Anatomical imaging (CT/MRI) for volumetric analysis for dosimetry will be required
- Theragnostic agent dose determination based on tumour size
- The patient will be required to stop interfering medications i.e. long-acting SS-analogues for 4-6 weeks; short-acting SS-analogues for 3 days
- Quality of life questionnaire completion will be required e.g. Karnofsky, ECOG and EORTC QLQ-C30 quality of life assessment

Dose determination – various methods exist (determined by Nuclear Physician):

- Methods:
  - Fixed dose
  - Dosimetric
- Modifiers:
  - Hepatic tumour burden (↓)
  - Bone marrow tumour burden (↓)

Admission:

- The patient will require admission
- The patient will be instructed on radiation personal hygiene
- Anti-emetics will be prescribed – Odansetron 8mg IV
- Analgesia will be given – Ibuprofen; Paracetamol
- Amino acid priming will be given for an hour prior to treatment to decrease renal reabsorption of the radiopharmaceutical. Each amino acid drip will be run in over 4 hours and the patient will require 4 of these – hence admission.
- The treatment will then be administered over 20-30min IV in 100-200ml NaCl 0.9%

Post-administration:

- Post administration scan or blood/urine collections for dosimetry (^{177}Lu-DOTA-Peptides) may be required.

Follow-up:

- Repeat blood counts will be required 4-6 weeks after each cycle (2 weeks before next cycle)
- Treatments can be repeated along with work-up (minimum of 4); more if cumulative dose is deemed favourable
- Repeat diagnostic imaging will be done 8 weeks after last cycle
- Follow-up laboratory and response monitoring after will also be required 3-6 months post therapy and repeated 6 monthly thereafter (this is lifelong)

Response targets – the following are response targets:

- Tumour marker reduction ≥ 50% of baseline
- Symptomatic response
- Imaging response according to validated standards (must be validated by two different modalities preferably)
- Improvement quality of life

Response outcomes:

- Maximum objective response in up to 46% of patients
- Time to disease progression ≥ 36 months
- Improved quality of life

When to stop therapy:

- Disease progression
- Protracted WHO grade 3 or 4 haematological, renal, hepatic toxicity (i.e. > 2-3 months)

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