NSW Cancer Institute / NSW Agency for Clinical Innovation Nuclear Medicine Network

NSW Lutate Therapy Referral and Protocol

for

Neuroendocrine Cancer Patients

by

Nuclear Medicine Department Lutate Services

at

St George and Royal North Shore Hospitals

January 2015

Background

Patients are diagnosed with neuroendocrine tumours (NETS) utilising multiple imaging modalities, blood tests, biopsies, surgery, or any combination of these methods. Final confirmation is made histologically.

Once NETs are diagnosed there is a range of initial treatment options which may be considered by the patient and their oncologist in their home LHD.

Lutate therapy in NSW is used when there is progression of NETs disease and existing growth-inhibiting therapies are no longer effective.

Peptide Receptor Radionuclide Therapy (PRRT) or Lutate Therapy is a specific therapy suitable for some but not all NETs patients, delivered by Nuclear Medicine departments. In the majority of cases, Lutate stabilises or improves disease that has previously been progressive, and some patients achieve remission.

Referral to NSW Lutate Services

NSW is supporting an evaluation of Lutate therapy at two sites; St George and Royal North Shore Hospitals.

Several hospitals in NSW have a NETs multidisciplinary team (MDT) or a broader cancer MDT. Once the MDT establishes that Lutate may be a valid treatment option, it is a requirement that their patients be referred to and reviewed by the NETs MDT at one of the two NSW Lutate Services.

When patients are referred to one of the two NSW Lutate Services, they will be added to a NETs MDT Register. A range of factors will inform the assignment of patients for assessment, including the capacity of each Centre, continuity of care and convenience for patients. Patients will need to meet nationally agreed patient selection criteria before Lutate treatment can be considered.

Multi-modality treatments may still be required during Lutate therapy. Any additional treatments during Lutate therapy should be discussed with the patient and their referring oncologist to determine whether there are other options closer to home, etc. It is expected that patients will return to the care of their referring oncologist post-Lutate therapy.

If Lutate therapy is not recommended at this time by the Lutate Service’s NETs MDT, the patient should be referred back to their oncologist with discussion around reasons for exclusion.

Lutate Services
St George Hospital - Lutate bookings clerk: 9113 3123

Royal North Shore Hospital - Lutate bookings clerk: 9926 4440

To be considered by the NETS MDT at St George or Royal North Shore Hospitals, the following results should accompany the patient to be assessed for Lutate suitability:

- Confirmation of diagnosis of NETs – biopsy results
- ^{68}Ga octreotate scan (^{111}In octreotide scan is an acceptable substitute if PET is not available)
- CT scan (chest/abdo/pelvis)
- Blood workup (including FBC, biochemistry, chromogranin level, hormone assays of blood and urine)

Patient Assessment Process

All patients being considered for Lutetium177-Dota-Octreotate (Lutate) therapy will:

- meet each of the suitability criteria listed below, and
- have no contraindications/exclusion criteria, and
- be recommended for Lutate therapy by the NETs MDT

Suitability criteria for Lutate Therapy

- Histologically proven NET of any origin
- Locally advanced and/or inoperable (metastatic) disease
- Failed first line systemic therapy
- Progressive disease demonstrated radiologically while on somatostatin analogue therapy or uncontrolled symptoms despite systemic therapy
- Presence of somatostatin-receptors on the known tumour lesions demonstrated by ^{68}Ga octreotate scan within past 6 months. The uptake of the NET lesions should be at least as high as normal liver uptake
- ECOG status 0-2
- Patient's written voluntary informed consent

Exclusion criteria

- Significant co-morbidity that is likely to interfere with the therapy.
- ECOG 3 or 4
- Uncontrolled congestive heart failure or carcinoid heart disease
- Patients unable to interrupt somatostatin analogue (SSA) therapy for the following periods:
    - Short-acting SSA: 12 hours before, and 12 hours after, Lutate.
    - Long-acting SSA: 4-6 weeks before Lutate

    - *(unless the tumour uptake is ≥ normal liver uptake on the ^{68}Ga octreotate scan during continued SSA treatment).*
- Life expectancy less than 12 weeks
- Pregnancy
- Renal impairment
    - (GFR < 40 ml/min/1.73m^2)
- Impaired bone marrow reserve:
    - Haemoglobin ≤ 9.0 g/dL;
    - WBC ≤ 2 x 10^9/L;
    - Absolute neutrophil count < 1.0
    - Platelet count ≤ 75 x 10^9/L.
- Hepatic impairment
    - Total serum bilirubin ≥ 75 micromoles/L or ≥ 1.5 x upper limit normal (unless Gilbert's syndrome)
    - Serum albumin ≤ 25 gm/L
- Discordant FDG uptake (with significant disease that is FDG avid but ^{68}Ga dotatate non-avid). In these patients, other systemic therapies are recommended.

Lutate Treatment

Lutate reconstitution
Lutetium-177 and peptide will be imported from IDB in Holland via Global Medical Solutions (GMS) at this time in line with other states, and delivered to St George and Royal North Shore Hospitals. Radiochemical purity is assayed prior to administration. Reconstitution of the Lu177-DOTA-octreotate is performed in the Nuclear Medicine department following the recommendations of the manufacturer/supplier (see attachment).

The therapy is administered over four cycles, 8 weeks (range 6-12 weeks) apart. The total treatment regimen takes approximately 32 weeks.

Prior to the day of Lutate therapy

- Once recommended for consideration of Lutate therapy by a NET MDT, the patient will attend the Nuclear Medicine department of the treating facility for a consultation with Nuclear Medicine staff

- **Investigations** Relevant investigations will be reviewed, or undertaken as appropriate, including blood tests (FBC, EUC, LFT), GFR assessment and cardiac imaging (if required). If not already performed, an FDG PET scan may also be required in patients with higher grades of disease to determine if there is any FDG-avid / ^{68}Ga dotatate non-avid disease

- **Radiosensitising chemotherapy** will be administered before, and after, each cycle of Lutate in all patients undergoing Lutate therapy, unless absolutely (or relatively) contraindicated in individual clinical situations. In general, this will comprise Capecitabine (Xeloda) 750mg bd administered for 1 week prior to, and 2 weeks following, Lutate therapy.

- **Somatostatin analogue treatment** can be continued in between treatments with radiolabelled somatostatin analogues. However, long-acting somatostatin analogues, such as Sandostatin LAR, should be discontinued at least 4-6 weeks before the treatment date and short-acting somatostatin analogues should be stopped the day before the treatment date, unless not clinically possible, and the uptake on the ^{68}Ga Octreotate scan during continued somatostatin analogue medication is sufficient (lesions ≥ normal liver). Treatment with short-acting somatostatin analogues can be resumed the day after the administration of Lutate

- As Lutate is not registered by the TGA, a SAS form signed by the Nuclear medicine physician should be completed and faxed to the TGA as well as GMS

On the day of Lutate therapy
The patient should not fast (a light breakfast is preferable) and should be well hydrated. All medication can be continued, except for somatostatin analogues (see above).

The patient will present to the Nuclear Medicine department and undergo:

- **Clinical review** (as relevant)

- **βHCG** test (if appropriate)

- **Cannulation** (taking care to ensure there is no risk of extravasation)

- **Premedication administration** To reduce the likelihood and severity of nausea and vomiting (secondary to the amino acid infusion), premedications are administered. These will vary according to local preference and availability but will typically comprise Dexamethasone (PO or IV) and a selective 5-HT_3 receptor antagonist (usually Granisetron, Ondansetron, or Tropisetron). If clinically indicated, Temazepam or Lorazepam may be administered for 2 days after treatment. In patients with (or at risk of) hyperkalaemia, PO resonium A (30mg) may be prescribed

- **Transmission scan** This is performed using a Co-57 sheet source and may be performed prior to each Lutate therapy, or prior only to the first patient's 1st therapy, according to local preference. Acquisition is performed using Triple Energy Window for scatter subtraction

- **Amino acid infusion** This is administered for renoprotection and is administered over 3-4 hours at 250ml/hr. Slower infusions (4-5hrs) should be done in patients with renal impairment. There is the option to use either an amino acid solution containing 25gm of lysine per litre and 25gm of arginine per litre (made in-house), or Baxter Synthamin containing 5.8 g Lysine and 11.5 g Arginine per litre

- **Lutate** At approximately 30 minutes after commencement of the amino acid infusion, 7.5-8GBq Lu-177-DOTA Octreotate (Lutate) is administered. Lutate is infused over 20-30minutes under the supervision of the Nuclear Medicine specialist. At the completion of the Lutate infusion, the amino acid infusion continues for a further 2-4 hours (as detailed above)

- **Scintigraphy** Gamma camera imaging is performed to permit renal dosimetry calculations. In general, a whole body image with 2 windows (DEW – dual energy window subtraction) will be done at 4 - 6 hours post administration. In addition, a SPECT/CT image with 2 windows (DEW) at 4 – 6 hours is also performed after each cycle. Additional imaging may be performed according to local preference. Renal dosimetry is calculated and recorded for each patient after each cycle of Lutate

Possible side effects

- **Nausea and vomiting** In the event of nausea or vomiting despite the premedication, patients will be treated with other anti-emetic drugs at the discretion of the physician, such as oral metachlopromide

- **Carcinoid Crisis** Patients who have been treated with somatostatin analogues previously are able to be treated with Octreotide acetate in the event of carcinoid crisis. Octreotide doses of 50-500 mcg, repeated as necessary administered by rapid IV injection for control of hypotension and other manifestations of carcinoid crisis. Prolonged IV infusions at 50 mcg/hour infused for 8-24 hours can be used, depending on the clinical condition of the patient

Post-Lutate treatments

- In between therapy cycles, the patient is reviewed by their treating medical oncologist who is responsible for their management

- **Blood tests** All patients will have haematology (FBC) and blood chemistry (EUC, LFT) evaluations 4 weeks after each treatment. Further blood samples must be collected within 2 weeks prior to the next Lutate administration. Serial Chromogranin A measurements will be done according to local protocols and referrer preference, as appropriate

- **Imaging** Following the fourth course of Lu-177 Octeotate therapy, a repeat ^{68}Ga dotatate scan will be obtained to assess treatment response. Additional ^{68}Ga dotatate scans may be done as clinically required or according to local preference. Restaging CT scans will be done at the discretion of the treating medical oncologist as per the standard care of patients with NET, typically 2-4 months after treatment. If FDG avidity was demonstrated at baseline, serial FDG studies may be warranted

- **Medications and chemotherapy** Somatostatin analogues and radiosensitising chemotherapy will be prescribed as detailed above

- **Safety reporting** Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of haematology and blood chemistry values, and the performance of physical examinations by the referring oncologist between cycles of Lutate therapy. Any adverse event thought related to Lutate will be recorded with the information forwarded to company supplying the Lu177-DOTA-Octreotate therapy in accordance with the TGA Special Access Scheme (SAS) requirements

- **Data collection** A database is maintained at each site which comprises a minimum agreed data set relevant to Lutate therapy. Information collected will be available for collation into the database to be developed by COSA and the NSW Cancer Institute