Pilot Study: Yttrium-90 DOTA-TOC Intra-arterial (IA) Peptide Receptor Radionuclide Therapy (PRRT) for Neuroendocrine Tumor

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INTRODUCTION

Peptides targeting the somatostatin receptor (SSTR), which is commonly overexpressed in Gastroenteropancreatic Neuroendocrine Tumours (GEP-NET). Peptide-receptor radionuclide therapy (PRRT) has been demonstrated to have a pronounced effect on radiographic progression disease free survival as well as likely improvement in overall mortality and quality of life. While only few side effects were reported, the dose limiting organs due to radioactive effects are bone marrow and the kidney.

Up to 75% of GEP-NET patients have liver metastases at time of diagnosis, and frequently liver metastases from GEP-NETs are often unresectable. It would be logical to deliver the radiopharmaceutical directly to the liver metastasis using hepatic intra-arterial infusion. Preliminary work with intra-arterial PRRT has been published using 90Y-DOTA-TOC demonstrating increased tumour uptake on PET imaging. There is a theoretical reason to use 90Y instead of 177Lu: the increase beta particle energy from 90Y is expected to be better in treating larger tumours.

Although PRRT is a targeted therapy in which only organs/tumours that express SSTRs will bind to the radiopharmaceutical, it is hypothesized that direct hepatic injection will achieve higher hepatic intratumoral concentrations of the radiopharmaceutical and hence providing more effective treatment of hepatic metastases and possibly reducing marrow and renal toxicity. Because of the theoretical benefit of administering 90Y-DOTA-TOC via the hepatic artery, we embarked on a Pilot study to determine whether or not IA administration results in decreased tumour size.

MATERIALS AND METHODS

This study was approved by the local institution review board (IRB), and informed written consent was obtained from all subjects. An Investigational New Drug application was approved by the Food and Drug Administration (FDA) for this study. Since July of 2017, 5 patients were treated on protocol. In total we plan to include 32 patients, and the primary endpoint is RECIST response of liver lesions.

- Inclusion criteria: Somatostatin receptor positive liver dominant metastatic neuroendocrine tumour, involving 10-70% of the liver. Progression over past 12 months with either a new lesion of 20% growth of an existing lesion. Stable extrahepatic disease is allowed. Not a candidate for surgical debulking.
- Exclusion criteria: Impaired renal, liver or bone marrow function. Prior external beam radiation therapy to the liver or more than 25% of the bone marrow. Prior PRRT treatment allowed.

Treatment: 85-115 mCi of 90Y-DOTATOC was administered through the common hepatic artery. All patients were treated with amino acid solution throughout the procedure for renal protection. Therapy was administered over 30 minutes.

Imaging correlate: In all patients, prior to treatment, 5 mCi of 68Ga-DOTATOC was administered intravenously and imaging was performed using PET/CT performed 90 minutes after injection. Additionally, concurrent with the intra-arterial administration of 90Y-DOTATOC, 5 mCi of 68Ga-DOTATOC was administered and PET/CT imaging was performed again 90 minutes after injection.

RESULTS

To date, five patients have been treated with intra-arterially administered 90Y-DOTATOC. All patients received 100-108 mCi of 90Y-DOTATOC.

The most common side effect was nausea and vomitting associated with the amino acid administration (all CTCAE grade 2 or less). One patient developed transient hyperbilirubinemia (Grade 2), anorexia (Grade 2), and abdominal pain (Grade 1). All resolved within 10 days of treatment.

Imaging follow-up for RECIST response is planned staring 12 weeks after treatment and has not yet been performed in any patients. The imaging correlate study demonstrated that there was evidence of receptor saturation in patients (**Figures 1-3**).

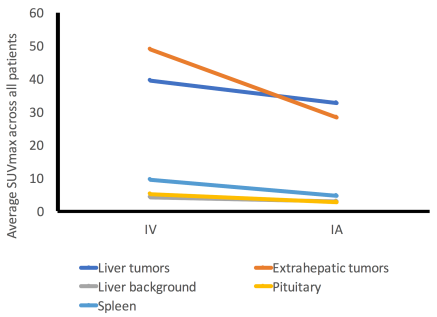

Figure 3: Change in average SUVmax across patients.

DISCUSSION

We have successfully treated five patients to date on our IA 90Y-DOTATOC pilot study. Overall the short term toxicity associated with the therapy appears minimal. One patient developed self limited hyperbilirubinemia and anorexia. No patients developed Grade 3 or higher CTCAE toxicity. Given that this trial follows patients for six months after treatment, we will not effectively evaluate for long term toxicity (secondary bone marrow malignancy).

The imaging correlate study demonstrated that there is significant receptor saturation associated with the therapy, likely due to the higher mass administered than is given with the imaging dose. The higher administered mass results in decreased uptake in all tissues (liver, spleen, pituitary, and tumors), but the uptake in the hepatic tumors decreases less than is seen in the extrahepatic disease. This suggests that although there is receptor saturation, there is still improved targeting to liver disease when performing the arterial administration. Due to the receptor saturation, in our next 10 patients we will compare a 30 minute to a 120 minute administration to determine if a longer administration can overcome the receptor saturation seen in our first five patients.

FUNDING

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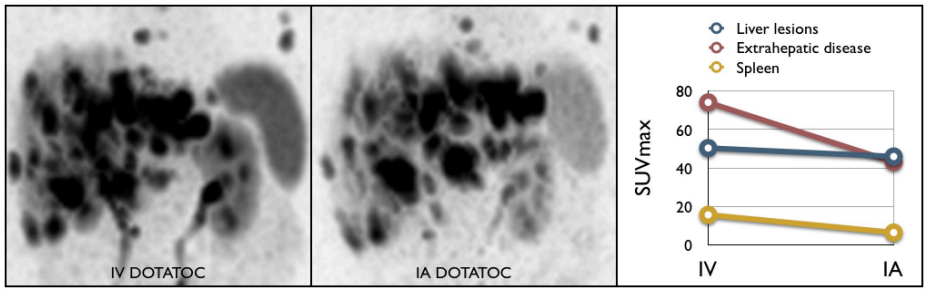

Figure 1: Second patient treated with IA 90Y-DOTATOC. All regions (spleen, liver disease and extraheptic disease) have decreased uptake during IA administration compared to IV administration. Splenic uptake fell 59%, extrahepatic disease uptake fell 71%, while the uptake in the liver lesions only fell 10%. This suggests that the receptors are being saturated although the hepatic administration does improve the uptake in hepatic tissue compared to extra-hepatic tissue.

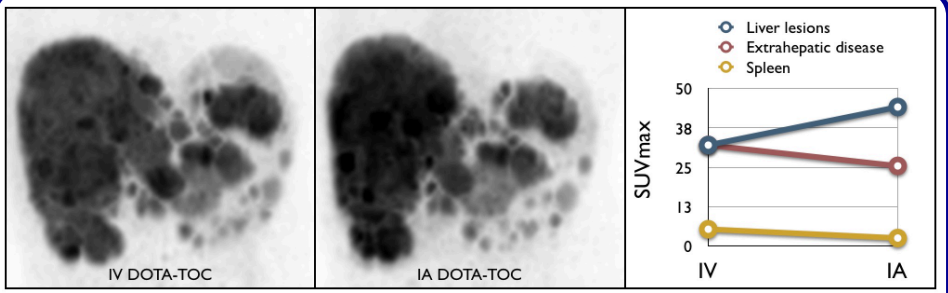

Figure 2: Third patient treated with IA 90Y-DOTATOC. Left image is the IV 68Ga-DOTATOC PETCT performed before the therapy. The middle image is the IA 68Ga-DOTATOC PETCT performed during the therapy. The chart demonstrates changes in the extrahepatic sites of diseases (20% reduction in uptake), liver lesions (36% increase in uptake), and spleen (11% reduction in uptake). This patient has nearly 70% liver involvement, which decreases receptor saturation.