Tailoring Radionuclide Therapy of Neuroendocrine Tumours

Halftime review seminar December 13, 2018

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Background

Neuroendocrine tumours (NETs) stem from specialized neuroendocrine cells present in virtually every epithelialized organ of the human body. The most common primary tumour sites are the small intestines, lungs and pancreas. NETs are generally slow-growing making them relatively resistant to chemotherapy and thereby, up until recently, difficult to treat. Most NET cells express the somatostatin receptor (SSTR) on the cell surface, a receptor that is involved in modifying the cells hormonal production and growth. Synthetic analogues of somatostatin (SSA) can be coupled to radioactive isotopes thereby opening the possibility of both imaging and treating the tumours in a targeted manner. Imaging is achieved by coupling the SSA to a gamma-emitting isotope such as $^{111}$In for SPECT-imaging, or $^{68}$Ga for PET-imaging. Radionuclide therapy for NETs is achieved by coupling the SSA to a beta-emitter, either $^{177}$Lu or $^{90}$Y, and is commonly known as peptide receptor radionuclide therapy (PRRT). The possibility, inherent to radiopharmaceuticals, of being able to both image and treat a tumour based on the same molecular target is known as theranostics. It gives us the opportunity to visualize the distribution of a systemic tumour treatment before it is given, which can be used both as a patient selection tool and a way of quantifying and predicting the absorbed dose (AD) delivered to tumours and risk organs.

PRRT with $^{177}$Lu-DOTATATE has been used for the treatment of NETs for over 15 years, in a few specialized centres. It was decided early on that four treatments with 7.4 GBq each was a safe and effective treatment, and efforts to personalize PRRT using the theranostic principles have been limited to even fewer centres. The present project describes work done by our group to further optimize PRRT using imaging and dosimetry.

Aims

To explore the feasibility of tailoring radionuclide therapy using image-based dosimetry in a prospective, phase II clinical trial studying the effects on efficacy and toxicity when using $^{177}$Lu-DOTATATE in the treatment of NET.

Methods

Patients with progressive, metastatic NET where offered treatment in the clinical trial. Only patients with a high receptor-expression in pre-treatment imaging were eligible. They received 7.4 GBq $^{177}$Lu-DOTATATE per treatment cycle, and the number of cycles was guided by the AD to the kidneys as calculated from the activity registered in post-treatment gamma camera images. All patients were treated up to a protocol-specified renal AD-limit, unless hindered by toxicity or tumour progression, with a select group of patients being offered to continue to a higher renal AD.
Results

Paper I
Here we present the results from an interim analysis performed after 51/100 patients had been included. At the time of the analysis, 22 of the 51 included patients had received treatment as planned, with a median follow-up of 28 months. There was a large inter-patient variability in the number of treatment cycles received within the protocol-specified AD limits, and a large intra-patient variability in the AD/cycle. In total, 73% of the patients received >4 cycles of treatment (the current standard), with no grade 3-4 renal toxicity observed.


Paper II
In the second paper, the image and dosimetry database from 199 treatment cycles was used to explore possible simplifications in the dosimetric method. A dosimetry method limited to one imaging time point per treatment cycle was found to be as accurate as the protocol-specified method with four imaging time points.


Paper III (in preparation)
In 68Ga-DOTATATE PET/CT images it is evident that the pituitary gland has a high expression of SSTR, which would lead to a potentially high AD during 177Lu-DOTATATE treatment. This, in turn, could result in clinically relevant reduction in pituitary function especially when maximizing the number of treatment cycles as is done in the current clinical trial. We are in the process of analysing pituitary function changes during follow-up for the patients included in the trial.

Paper IV (in planning)
One obvious missing point in the above cited papers is the aspect of tumour AD as part of the tailoring strategy. There is no international consensus, however, on the best method to use to determine tumour AD in radionuclide therapy, and only scarce data on the dose-response relationship. A semi-automatic dosimetric method is being developed which will then be applied to patient images to estimate tumour dose and its relationship to tumour response.

Implications
Tailoring PRRT using dosimetry means to maximize the AD to the tumour while maintaining the AD to risk organs below the threshold for toxicity. There are many rocks on this road, however, such as an unknown dose-response relationship for both tumour and risk organs, non-standardized dosimetric methods and a disease with a low incidence. Despite these difficulties, we have designed a clinical trial that will be able to advance knowledge in some of these areas thereby contributing to the optimization of this treatment modality for future patients.