Retrospective phase II study of efficacy and safety of ^{177}Lu-DOTATOC Peptide Receptor Radiotherapy in patients with advanced neuroendocrine tumours

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Background

Expression of somatostatin receptors of various sub-types is common in differentiated metastasized neuroendocrine tumours (NET) [1], rendering them amenable to peptide receptor radiotherapy (PRRT) with radiolabelled somatostatin analogues (SSA). To date, '^{90}Y-DOTATOC', '^{177}Lu-DOTATATE' and '^{177}Lu-DOTATOC' are used therapeutically. This study was performed to evaluate efficacy and safety of '^{177}Lu-DOTATOC' as agent PRRT of advanced neuroendocrine tumours.

Material and methods

Fifty-six subjects with metastasized and progressive NET (50% gastroenteral, 26.8% pancreatic, 23.2% other primary sites) treated consecutively with ^{177}Lu-DOTATOC were analysed retrospectively. Subjects were administered ^{177}Lu-DOTATOC (mean 2.1 cycles; range_1-4) as 7.0GBq (median) doses at three-monthly intervals. Efficacy was analysed using CT and/or MRI according to RECIST 1.1 criteria and results were stratified for the number of administered cycles and the primary tumour origin.

Table 1: Patients characteristics [2]

		All	PRRT =1	PRRT > 1
Number of patients		56	24	32
Age at enrolment	Mean [StDev]	64.4 [13.9]	65.1 [14.0]	64.0 [14]
Gender	female	27	10	17
	male	29	14	15
Primary tumour (%)	pancreas	15 (27)	6 (25)	9 (28)
	gastro-intestinal	28 (50)	13 (54)	15 (47)
	Other (CUP, lung, others)	13 (23)	5 (20)	8 (25)
KPS	Mean [StDev]	81.2 [18.2]	70.4 [21]	89.4 [10.1]
Admin.activity, cum.(GBq)	Mean [StDev]	13.7 [7.3]	6.7 [1.8]	18.5 [5.3]

Results

In the total population (A), median progression-free and (PFS) overall survival (OS) was 17.4 and 34.2 months, respectively. Repeatedly treated patients had an overall PFS of 32.0 months for all (B), 34.5 months for gastroenteropancreatic 'NET' (GEP-NET) (C), and 11.9 months for other 'NET' (D). Objective response rate (ORR) (complete or partial) was 33.9%, 40.6%, 54.2%, and 0% for populations A, B, C, and D, respectively, while disease control rate (DCR) was 66.1%, 93.8%, 100%, and 75%. A high number of complete responses (CR) (16.1%, 18.8% and 25.0% for populations A, B and C) was observed, 78% of which were maintained through the follow up. 14% of subjects required more than one cycle to induce an initial response. In 32% of responders, it took four to eight months from the first 'PRRT' cycle before an initial response could be documented.

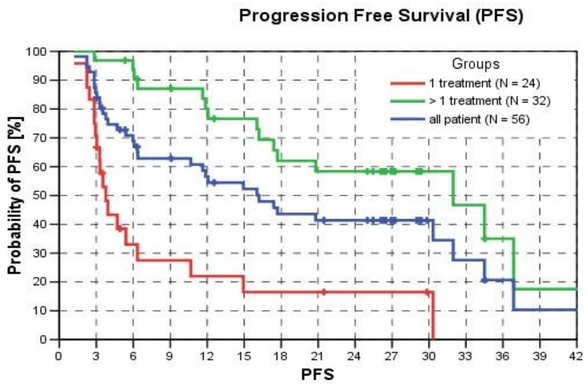

Figure 1: Kaplan-Meier estimates of PFS depending on number of ^{177}Lu-Dotatoc PRRT cycles (ALL NET)

In 47% of objective responders it took more than 8 months from the start of PRRT until an objective response occurred. No SAE, and only a single case (1.8%) of self-limiting grade 3 myelotoxicity was observed. No renal toxicity was found, although 19.6% of subjects had mild renal insufficiency at baseline.

Table 2: Previous PRRT monotherapy studies in mNET [3,4,5,6,7,8,9,10]

Reference	Compound	Primary tumor	Mean dose (GBq)	Mean cycles (N)	ORR (%)	CR (%)	DCR (%)	PFS (M)	OS (M)
Waldherr 2001 [3]	^{90}Y-TOC	All NET	6 / m²	4	24	2	85	> 26	> 24
Imhof 2011 [4]	^{90}Y-TOC	All NET	3.7/ m² * cycle	2 (1- 10)	34.1	0.6	39.3	NA	NA
Kwekkeboom 2008 [5]	^{177}Lu-TATE	**All NET**	**28.7**	**4**	**29.3**	**1.6**	**80.3**	**33**	**46**
Bodei 2011 [6]	^{177}Lu-TATE	**All NET**	**25.2 – 26.4**	**4 - 6**	**29**	**2**	**82**	**36**	**36 >**
Sansovini 2013 [7]	^{177}Lu-TATE	P-NET (all)			29	8	81	29	> 30
		> Full dose	27.8	5	39	12	85	> 30	> 30
		> Red. dose	18.5	5	19	4	77	20	> 30
Ezziddin 2014 [8]	^{177}Lu-TATE	P-NET	32	4	60	0	85	34	53
Paganelli 2014 [9]	^{177}Lu-TATE	GE-NET	18.4 – 25.7	5	7	7	84	36	> 60
Romer 2014 [10]	^{177}Lu-TOC	All NET	13.5	2	NA	NA	NA	NA	45.5
Present study	^{177}Lu-TOC	All NET	13.1	2.1	33.9	16.1	66.1	17.4	33.9
	1 cycle	All NET	6.9	1	25.0	12.5	29.2	3.8	3.9
	> 1 cycle	**All NET**	**18.5**	**2.6**	**40.6**	**18.8**	**93.8**	**32.0**	**34.7**

Conclusions

^{177}Lu-DOTATOC is a novel agent for PRRT with major potential to induce objective tumour responses and sustained disease control in progressive neuroendocrine tumours, even when administered in moderate activities. The observed safety profile suggests a particularly favourable therapeutic index, including in patients with impaired bone marrow or renal function, which reflects a uniquely low uptake of ^{177}Lu-DOTATOC by normal organs.

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