1228 ORAL

Peptide receptor radionuclide therapy (PRRT) with [IN-111-DTPA^0]octreotide (In-111-OC) in rats bearing the pancreatic somatostatin receptor (SSR) positive tumor CA20948

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Purpose: Lesions containing SSR in rats and in man can be visualized in vivo using In-111-OC. This radioligand is internalised via the SSR and In-111 has a long tumoral residence time, e.g. >700 h in humans. PRRT with high doses of In-111-OC was investigated in SSR-positive tumor-bearing rats.

Methods: Exp 1: CA20948 cells were injected into the portal vein on day 0, followed by 370 MBq In-111-OC (0.5 mg) per rat on day 1 and 8. Control rats received 0.5 mg only "cold" DTPA-Octreotide (OC). In Exp 2 the interaction of SSR and radioligand was blocked by 1 mg octreotide (octr) sc 30 min prior to the radioligand. The effect of 1 mg octr alone was also investigated. The rats were sacrificed on day 18 (Exp 1) or 21, and tumor colonies in the liver counted. Exp 3 was done as Exp 1 using SSR negative CC531 colon carcinoma cells.

Results are given in the table.

Conclusion: Peptide receptor radionuclide therapy with [In-111-DTPA^0]octreotide is effective and SSR-mediated.

Exp	Tumor colonies in liver				No rats
	0	1–20	21–100	>100	
1 OC	–	2	2	2	6*
In-111-OC	4	2	–	–	6
2 octr	–	–	–	6	6*
In-111-OC + octr	–	4	1	–	5*
In-111-OC	3	3	–	–	6
3 OC	–	–	3	3	6
In-111-OC	–	–	2	4	6

*: $p < 0.01$ vs In-111-OC; Mann-Whitney u-test.

1229 ORAL

Somatostatin receptor scintigraphy (SSRS) in GEP-tumors

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Purpose and Methods: Many human neuroendocrine tumors express somatostatin receptors and can be visualized in vivo with SSRS. A blinded, cost-effectiveness study was performed comparing SSRS and conventional imaging techniques as applied in the routine setting of the localization of GEP-tumours.

Results: Carcinoids: Calculating sensitivities for conventional imaging and SSRS, based on the total number of lesions visualised by any technique, 92% of lesions in 96% of patients were demonstrated with SSRS. Comparable percentages were found by others, who also report additional lesions in about a third of patients. The cost-effectiveness study, combining only SSRS with chest X-ray and upper abdominal ultrasound, led to the detection of lesions in all patients in whom with any means they could be demonstrated. The cost of this imaging strategy was higher than that of conventional imaging only. The benefits, however, were the detection of at least one lesion in 15% of patients in whom with conventional imaging only no abnormalities were found and a doubling of the number of lesions. Gastrinomas: SSRS demonstrated lesions in 11/12 (92%) patients. Previously unrecognized sites were found in 5 of 12 patients (42%). The combination of SSRS and CT scanning of the upper abdomen had the highest sensitivity in patients with gastrinomas. The relatively high cost is outweighed by demonstrating a resectable tumor. Insulinomas: SSRS demonstrated tumour localizations in 10/24 (42%) patients. The highest yield against the lowest cost is obtained if SSRS is only performed if CT scanning fails to demonstrate the tumor. Pheochromocytomas: 13 of 15 (87%) pheochromocytomas were somatostatin receptor positive in vivo. Discrepancies between SSRS and MIBG scintigraphy in the staging of malignant pheochromocytomas have been observed. Further studies are required.

Conclusion: SSRS is the first localization technique for GEP-tumours, except for insulinomas. **Future:** Treatment with In-111 and Y-90 coupled somatostatin analogues has been initiated and may prove valuable in inoperable patients with somatostatin receptor positive tumors.

1230 ORAL

Peptide receptor therapy with ^{111}IN-DTPA-octreotide (OC)

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Purpose: In a phase 1 study, 20 end-stage patients with mainly neuroendocrine tumours were investigated. The emission of Auger and conversion electrons by OC is used to induce an anti-proliferative effect.

Methods: The typical doses per administration were 6–7 GBq ^{111}In labeled to 40 μg DTPA-octreotide, given with 2 to 3 weekly intervals and a maximum of 12 administrations.

Results: No major side effects were noticed in the first treated patient after a cumulative dose of 25 GBq and a follow-up interval of 2 years, which is so far the longest follow up period. In the other patients no major side-effects were observed as well, although in 2 patients a transient thrombocytopenia and in most patients a decrease in lymphocyte-subsets without clinical symptoms have been found. No clinically relevant changes in kidney function were observed. Impressive effects on the clinical condition and on hormone or tumour marker production were observed, though in some patients temporary because of end-stage disease. Also, anti-proliferative effects have been noticed. Of all 20 patients with progressive disease, i.e. unequivocal increase in tumour-volume according to CT or MRI for six months prior to the start of OC therapy, in 12 patients this treatment resulted in either stable disease or actual tumour shrinkage up to 65%.

Conclusions: So far a response to treatment with OC, based on antiproliferative effects and a lowering of tumour markers in serum and/or urine, has been obtained if 1. the cumulative therapeutic dose of OC was at least about 450 mCi (17 GBq) and 2. tumour uptake was at least grade 2. **Future:** Radiotherapeutic use of radionuclides with higher energies of β-particles, e.g. ^{90}Y, coupled to DOTA-chelated Tyr-3-Octreotide, will lead to higher radiation doses in a larger part of the tumour because of their more appropriate tissue-penetration. Thus, tumours with an inhomogeneous distribution of peptide receptors may then respond favourably.

1231 ORAL

Telomerase activity in benign and malignant human thyroid disorders

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Introduction: Accumulating evidence has indicated that telomerase is stringently repressed in normal human somatic tissues but reactivated in cancers and immortal cells, suggesting that activation of telomerase activity may play a role in carcinogenesis. In this work, telomerase activities in benign and malignant human thyroid disorders were evaluated.

Methods: Telomerase activities were examined in 62 frozen samples obtained from patients with benign and malignant thyroid nodules. Samples diagnosed for specific pathology were confirmed histologically. Telomerase activity assay was performed with a PCR-based telomeric repeat amplification protocol (Science 266: 2011, 1994).

Results: Telomerase activity was detectable in 2 of 14 (14%) nodular hyperplasia, 4 of 14 (29%) adenoma, 12 of 23 (52%) papillary carcinoma and 10 of 11 (91%) follicular carcinoma tissues. Most of the papillary and follicular cancers with advanced stage (stage III or IV) were positive for telomerase activity. On the other hand, cancers shown negative for telomerase activity were mostly in early stage (stage I). There is no significant correlation of telomerase activity with the level of thyroid globulin or with patient age.

Conclusion: The presence of telomerase activity is correlated with the prognosis of malignant thyroid disorders. These results suggest that telomerase activity may play a role during thyroid tissue carcinogenesis, and may serve as an aid in the diagnosis of malignant thyroid disorder.

1232 ORAL

The value of scintigraphy for diagnosis in differentiated thyroid cancer is questionable

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There is a continuing controversy about the value of scintigraphy for preop-