14.1

A High Activity Rhenium-186 HEDP with Peripheral Blood Stem Cell Support Phase I Study in Hormone Refractory Prostate Cancer Patients with Skeletal Metastases

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Aim: This study was designed to find the maximum tolerated activity of Re 186 HEDP which could be given with peripheral blood stem cell support (PBSCS) to ablate or prevent skeletal metastases from prostate cancer. Previous studies have identified thrombocytopenia as the dose limiting toxicity at a level of 3.0 GBq.

Methods: Twenty five patients with progressive hormone refractory prostate cancer metastatic to bone received an intra-venous injection of Rhenium-186 HEDP followed 14 days later by the return of pre-harvested peripheral blood stem cells (PBSC). Prescribed activities ranged from 2.5 GBq to 5.0 GBq. Unacceptable toxicity was defined as grade III haematological toxicity, lasting at least 7 days duration, or grade IV haematological toxicity of any duration or any serious unexpected toxicity. PSA measurements and bone scintigraphy were performed at 6 weeks and three monthly intervals.

Results: One patient with Grade III thrombocytopaenia occurred at 5.0 GBq and another in a second group of 3 patients at the same activity level. Both recovered within 10 days in both cases indicating that 5.0 GBq is the maximum tolerable activity.

In the group of 17 patients who received between 3.0 and 4.9 GBq, 9 developed no new metastases in their latest bone scan between 5.5 weeks and 2 years post therapy. In 7 patients between 14% and 70% of their metastases disappeared. PSA reductions of 50% or more, lasting at least 4 weeks, were seen in 5 of the 25 patients (20%) who received more than 3.5 GBq of Rhenium-186 HEDP.

Conclusions: The maximum tolerated activity of Re 186 HEDP with PBSCS is 5.0 GBq. Rhenium 186 HEDP therapy using higher activities can prevent the onset of new metastases and can also ablate some of those already present in a substantial number of patients with refractory hormone refractory prostate cancer.

14.2

Radioastatine and Radioiodine Uptake Characterization in Sodium Iodide Symporter-Expressing Cell Lines

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Aim: The sodium iodide symporter (NIS) has been recognized as an attractive target for cancer gene therapy. Here we investigated NIS-mediated transport of the high LET α-emitter astatine, ^{211}At, in comparison to radioiodine.

Methods: A constitutive expression vector harbouring the human NIS cDNA was used in combination with reporter gene vectors for transient transfection of 13 different human cancer cell lines. Radioiodine uptake was measured as well as transfection efficiencies. Six stable

NIS-expressing cell lines (3 derived from thyroid carcinomas, 2 colon carcinoma, 1 glioblastoma) were generated by antibiotic selection. NIS expression was monitored by immunohistochemistry and RT-PCR. Subsequently the radioastatine and radioiodine uptake characteristics of genetically modified cells were studied in comparison to the respective control cells. After xenotransplantation in nude mice in vivo tumour imaging by scintigraphy and biodistribution studies following organ removal were performed.
Results: Transient transfection of NIS cDNA led to high specific sodium perchlorate-sensitive radioiodine uptake in NIS-expressing cells that roughly correlates to transfection efficiencies. Similarly, stable NIS-expressing cell lines were able to concentrate high levels of radioiodine and in addition showed comparable transport capacity for radioastatine. Accumulation of ^{211}At was inhibited by sodium perchlorate like iodide uptake and displayed dependency on extracellular Na^+- and I^--ions as well. Compared to wash-out experiments in cell culture the effective half life of radioiodine and radioastatine in vivo was significantly prolonged. Preliminary dose calculations by MIRD concepts indicated higher tumour radiation doses for ^{211}At compared to ^{131}I.
Conclusion: Tumour cells of different origins transfected with the NIS-expression vector specifically and significantly take-up radioiodine and radioastatine in vitro and in vivo. The data provide direct evidence that the NIS efficiently transports the high LET α-emitter ^{211}At with characteristics comparable to radioiodine uptake. In addition, ^{211}At may direct significantly higher radiation doses to tumours than ^{131}I by this route and thus may represent a promising alternative for future NIS-mediated cancer gene therapy.

14.3

The Dresden In-Stent Restenosis Radiation Trial (DIRRT) with Liquid-Filled ^{188}Re Balloon

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Aim: In some studies intracoronary radiation therapy (IRT) to minimize the restenosis rate after PTCA proved to be effective. We evaluated the performance, safety and effectiveness of IRT with ^{188}Re-perrhenate filled into a standard PTCA balloon. This kind of IRT allows a self-centering homogenous dose distribution to the vessel wall.
Methods: 107 patients (pts) with a mean age of 63 years (81 m, 26 fm) with in-stent restenosis (type B in 39 %, type C in 61 %) and proven ischemia were included. After routine re-PTCA with or without additional stent implantation a second standard balloon was placed into the PTCA area and filled with ß$^-$-emitting liquid ^{188}Re at 3 atm. Irradiation time was 525 +/- 167 sec to achieve a dose of 30 Gy at 0.5 mm depth of the vessel wall.
Results: In only one procedure there was a disconnection of the ^{188}Re containing system and the catheter but no contamination of the cath table or lab was measured. In 16 coronaries 21 stents were additionally implanted. In the follow-up 4 stent thromboses (1 day, 37 days, 2 x 6 months) with subsequent myocardial infarction were noticed, all in pts with additionally implanted stents. 57 pts had control angiography after 4 to 6 months after therapy and 41 after one year. Restenosis (stenosis > 50 % of luminal diameter) was shown in 9 out of 12 pts (75 %) with additionally implanted stents but only in 4 out of 24 pts (17 %) with PTCA alone. Reocclusion was noticed in 3 (25 %) pts with additional stent but only in 1 pt (4 %) without. No re-restenosis occured in 20 patients which were without finding after 6 months.