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OctreoTher™: Ongoing Early Clinical Development of a Somatostatin-Receptor-Targeted Radionuclide Antineoplastic Therapy

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Key Words
Breast cancer · Clinical studies · DOTATOC · Neuroendocrine tumors · OctreoTher™ · Peptide radiotherapy · Small cell lung cancer · Somatostatin receptor · Yttrium-90

Abstract
OctreoTher™ (^{90}Y-DOTA-D-Phe^{1}-Tyr^{3}-octreotide, a.k.a. ^{90}Y-SMT 487) consists of a somatostatin peptide analogue (Tyr^{3}-octreotide), coupled with a complexing moiety (DOTA), and labeled with a tightly bound beta-emitter (yttrium-90). By targeting somatostatin receptor-positive tumors (as imaged by OctreaScan®) it may deliver a tumoricidal dose of radiation. Phase I clinical trials, conducted in patients with neuroendocrine tumors, established the safety and tolerability of the dose selected for further study and demonstrated the capacity of OctreoTher to deliver radiation doses to tumors that resulted in significant neuroendocrine tumor shrinkage. Novartis-sponsored phase II studies will soon begin to test the efficacy of OctreoTher in breast and small cell lung cancer. A fixed-dose regimen of 120 mCi/cycle × 3 cycles administered with concomitant amino acid infusion has been chosen for the study. Phase I data and published literature support that this fixed dose regimen will be safely tolerated.

Introduction

OctreoTher™ is a Novartis development compound currently in phase I multicenter clinical trials to test its potential as a somatostatin-receptor-targeted radionuclide antineoplastic therapy. These studies are sponsored in cooperation with Mallinckrodt Medical Incorporated. The overall goal of this development program is to demonstrate the disappearance or significant shrinkage of somatostatin receptor positive solid tumors (e.g. neuroendocrine, breast or small cell lung tumors) in the absence of clinically apparent toxicity to major organ systems in patients receiving OctreoTher. Data from the Novartis-sponsored ongoing phase I study in neuroendo-

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cal studies not sponsored by Novartis have provided support for the choice of regimen to be tested in a multicenter phase II study. This phase II study, to begin this year at 12 centers in Australia, the United States and Europe, will examine the safety and efficacy of the chosen regimen in approximately 60 patients with breast and small cell lung cancer.

Preclinical Rationale

OctreoTher (^{90}Y-DOTA-D-Phe^{1}-Tyr^{3}-octreotide, a.k.a. ^{90}Y-SMT 487) consists of a somatostatin peptide analogue (Tyr^{3}-octreotide), coupled with a complexing moiety (DOTA), and labeled with a tightly bound beta-emitter (yttrium-90). By targeting somatostatin receptor-positive tumors (as imaged by OctreoScan®) it may deliver a tumoricidal dose of radiation. Yttrium-90 (^{90}Y) is a high-energy beta-emitter with a mean path length of 5 mm in tissue and a physical half-life of 64.1 h. SMT 487 binds with high affinity to somatostatin receptors (subtypes 2 and 3) and retains both its binding properties and its physiological function when labeled with ^{90}Y.

The preclinical rationale for the use of OctreoTher is based on evidence that:

(1) OctreoTher accumulates in somatostatin receptor-containing tissue or tumors.

(2) Receptors remain present and able to bind OctreoTher during treatment.

(3) Tumor regression was demonstrated in vivo [1].

In tumor-bearing nude mice, OctreoTher was effective in somatostatin receptor-positive tumors, a single dose both shrinking the tumor and prolonging survival. A single dose in rats caused pancreatic tumors to disappear without regrowth. No difference in tumor regression was seen between perilesional, intraperitoneal or intravenous administration of OctreoTher, so the more convenient intravenous application was selected for clinical development.

Phase I Clinical Studies of Neuroendocrine Tumors

Phase I clinical trials, conducted in patients with neuroendocrine tumors, established that following an intravenous infusion, plasma radioactivity disposition of OctreoTher was multiphasic (terminal $t_{½}$ ~8.6 h). Unbound radioactivity was excreted in urine. By 24 h post-The rapid clearance of OctreoTher from the circulation gives this radiopharmaceutical a major advantage over radiolabeled antibodies, whose long plasma half-lives (several days) cause higher levels of whole-body irradiation. OctreoTher is not significantly taken into erythrocytes. A correlation between creatinine clearance and total body radioactivity clearance was observed reflecting that the kidney is the principal drug eliminating organ and suggesting that OctreoTher is not recommended in subjects whose creatinine clearance is less than 40 ml/min. Radioactivity exposure was mainly to kidney, spleen, urinary bladder wall, and tumors. Gamma scintigraphy with ^{111}In-pentetreotide (OctreoScan) may be used to identify OctreoTher-binding tumors. The relative biodistribution and pharmacokinetic profile of OctreoTher was not altered by changes in the absolute peptide dose over the range of 50–500 µg. Notably, concomitant administration of amino acids reduced renal radioactivity uptake without altering tumor uptake in a phase I study. Cationic amino acids appear to be responsible for the 'blocking' of renal tubular uptake of proteins or peptides [2, 3]. A variety of other maneuvers have been attempted, so far, without success in further lowering the relative renal uptake of OctreoTher.

Phase I clinical trial results support the safety and tolerability of the dose selected for further study. The organ of dose-limiting toxicity was confirmed to be primarily the kidney and secondarily the hematopoietic system. Acute radiation nephritis may appear as a syndrome of hypertension, proteinuria and anemia presenting up to a year after the causal radiation exposure [4]. Furthermore, these studies demonstrated the capacity of OctreoTher to deliver radiation doses to tumors that resulted in significant neuroendocrine tumor shrinkage. The planned phase II study will assess the safety and anti-tumor activity of OctreoTher in refractory small cell lung cancer and advanced metastatic breast cancer.

Planned Phase II Clinical Study of Small Cell Lung and Breast Cancers

Small cell lung cancer (SCLC) comprises approximately 18% of all primary lung cancer, virtually all of the tumors bearing somatostatin receptors [5–8]. Although SCLC is highly sensitive to radiation, coexistent lung tissue damage and the early occurrence of distant metastases limit the utility of external beam irradiation. Resistance

Prognosis is correspondingly poor; approximately 95% of those afflicted succumbing to their disease, regardless of therapy or earliness of diagnosis. Hence, OctreoTher, by providing systemic, yet targeted irradiation to metastatic SCLC, should provide a much-needed, additional therapeutic modality.

Breast cancer is the commonest malignancy among women. The prognosis is variable and first- and second-line therapies are well established. Approximately 70% of primary breast cancers express somatostatin receptors [5, 9–11]. Patients with advanced metastatic breast cancer, who are shown by OctreoScan to have high somatostatin receptor levels, may benefit from therapy.

Primary Study Objectives

1 To evaluate the efficacy of OctreoTher in advanced metastatic breast cancer and refractory small cell lung cancer as measured by tumor response rate (PR + CR SWOG criteria).
2 To evaluate the safety of OctreoTher as measured by the rate of (mild/moderate/severe/life-threatening) adverse events, and serious adverse events and the monitoring of selected laboratory evaluations.

Secondary Study Objectives

1 To measure the overall survival of patients treated with OctreoTher.
2 To evaluate the effect of OctreoTher on quality of life as measured by the EURO-QOL EQ-5D.
3 To assess the frequency of tumors which are positive (tumor uptake > liver uptake) for OctreoScan within the screened population.

Data from Non-Novartis-Sponsored Studies in the Literature

Investigators not affiliated with Novartis have produced and conducted clinical trials with a compound, which appears to be identical to OctreoTher, called Yttrium-90 DOTATOC [12–14]. To summarize the renal toxicity reported by these investigators, for purpose of comparison, 24 patients received $\leq$7,400 MBq/m^2. This limit (7,400 MBq/m^2) corresponds to 200 mCi/m^2, and, using the average reported BSA of these 24 patients 368 mCi per patient which was safe and tolerated. Some, but not all, of the administered cycles were in the presence of concomitant amino acid infusion. There was no adjustment for renal dosimetry, which was also not performed/reported. Four patients, who all received >7,400 MBq/m^2, developed renal toxicity: 2 patients who received cumulative doses of 360 and 385 mCi, respectively, showed stable renal insufficiency; 2 other patients who received 380 and 410 mCi, respectively, showed complete renal failure (dialysis dependent). None of the 4 patients who developed renal toxicity received any concomitant amino acid infusion. Thus, all doses at or below 360 mCi administered with concomitant amino acids appear to have been tolerated safely.

Conclusion

Novartis-sponsored phase II studies will soon begin to test the efficacy of OctreoTher in breast and small cell lung cancer. A fixed-dose regimen of 120 mCi/cycle × 3 cycles administered with concomitant amino acid infusion has been chosen for the study. Phase I data and published literature support that this fixed dose regimen will be safely tolerated.

1 Stolz B, Weckbecker G, Smith-Jones P, et al: The somatostatin receptor-targeted radiotherapeutic [^{90}YDOTA-D-Phe^{1},Tyr^{3}]octreotide (^{90}Y-SMT 487) eradicates experimental rat pancreatic CA 20948 tumours. Eur J Nucl Med 1998;25:668–674.
2 Hammond PJ, Wade AF, Gwilliam ME, et al: Amino acid infusion blocks renal tubular uptake of an indium-labelled somatostatin analogue. Br J Cancer 1993;67:1437–1439.
3 Mogensen CE, Solling K: Studies on renal tubular protein reabsorption: partial and near complete inhibition by certain amino acids. Scand J Clin Lab Invest 1977;37:477–486.
4 Maher J: Section 6: Diseases of the kidney and urinary tract, Part 8: Radiation Nephropathy; in Masary SG, Glassock RJ (eds): Textbook of Nephrology. Baltimore, Williams & Wilkins, 1989.
5 Krenning EP, Kwekkeboom DJ, Bakker WH, et al: Somatostatin receptor scintigraphy with [^{111}In-DPTA-D-Phe^{1}]- and [^{123}I-Tyr^{3}]-octreotide: The Rotterdam experience with more than 1,000 patients. Eur J Nucl Med 1993;20:716–731.
6 Kwekkeboom DJ, Kho GS, Lamberts SJ, et al: The value of octreotide scintigraphy in patients with lung cancer. Eur J Nucl Med 1994;21:1106–1113.
7 O'Byrne KJ, Ennis JT, Freyne PJ, et al: Scintigraphic imaging of small cell lung cancer with [^{111}In]pentetreotide, a radiolabelled somatostatin analogue. Br J Cancer 1994;69:762–766.
8 Bombardieri E, Crippa F, Cataldo I, et al: Somatostatin receptor imaging of small cell lung cancer by means of ^{111}In-DPTA octreotide scintigraphy. Eur J Cancer 1995;31A:184–188.
9 Bootsma AH, van Eijck CHJ, Schouten KK, et al: Somatostatin receptor-positive primary breast tumors: Genetic, patient and tumor characteristics. Int J Cancer 1993;54:357–362.
10 Van Eijck CHJ, Krenning EP, Bootsma A, et al: Somatostatin receptor scintigraphy in primary breast cancer. Lancet 1994;343:640–643.
11 Evans AA, Crook T, Laws SAM, et al: Analysis of somatostatin receptor subtype mRNA expression in human breast cancer. Br J Cancer 1997;75:798–803.
12 Otte A, Herrmann R, Heppler A, et al: Yttrium-90 DOTATOC: First clinical results. Eur J Nucl Med 1999;26:1439–1447.
13 Otte A, Jermann E, Behe M, et al: DOTATOC: A powerful new tool for receptor-mediated radionuclide therapy. Eur J Nucl Med 1997;24:792–795.
14 Otte A, Mueller-Brand J, Dellas S, et al: Yttrium-90-labelled somatostatin-analogue for cancer treatment. Lancet 1998;351:417.