Abstract

Purpose: The somatostatin analogue [DOTA\(^0\), Tyr\(^3\)]octreotide (DOTATOC) has previously been labeled with low linear energy transfer (LET) \(\beta\)-emitters, such as \(^{177}\)Lu or \(^{90}\)Y, for tumor therapy. In this study, DOTATOC labeled with the high-LET \(\alpha\)-emitter, \(^{213}\)Bi, was evaluated.

Experimental Design: The radiolabeling, stability, biodistribution, toxicity, safety, and therapeutic efficacy of \(^{213}\)Bi-DOTATOC (specific activity 7.4 MBq/\(\mu\)g) were investigated. Biodistribution studies to determine somatostatin receptor specificity were done in Lewis rats at 1 and 3 hours postinjection. Histopathology of various organs was used to evaluated toxicity and safety. Therapeutic efficacy of 4 to 22 MBq \(^{213}\)Bi-DOTATOC was determined in a rat pancreatic carcinoma model.

Results: Radiolabeling of the \(^{213}\)Bi-DOTATOC was achieved with radiochemical purity \(\geq 99.9\%\) and an incorporation yield \(\geq 99.9\%\). Biodistribution data showed specific binding to somatostatin receptor – expressing tissues. Administration of free \(^{213}\)Bi, compared with \(^{213}\)Bi-DOTATOC, resulted in higher radioactivity accumulation at 3 hours postinjection in the kidneys (34.47 \(\pm\) 1.40% injected dose/g (ID/g) versus 11.15 \(\pm\) 0.46%, \(P < 0.0001\)) and bone marrow (0.31 \(\pm\) 0.01% ID/g versus 0.06 \(\pm\) 0.02%, \(P < 0.0324\)). A significant decrease in tumor growth rate was observed in rats treated with \(>11\) MBq of \(^{213}\)Bi-DOTATOC 10 days postinjection compared with controls (\(P < 0.025\)). Treatment with \(>20\) MBq of \(^{213}\)Bi-DOTATOC showed significantly greater tumor reduction when compared with animals receiving \(<11\) MBq (\(P < 0.02\)).

Conclusions: \(^{213}\)Bi-DOTATOC showed dose-related antitumor effects with minimal treatment-related organ toxicity. No acute or chronic hematologic toxicities were observed. Mild, acute nephrotoxicity was observed without evidence of chronic toxicity. \(^{213}\)Bi-DOTATOC is a promising therapeutic radiopharmaceutical for further evaluation.

Somatostatin is a 14-amino-acid peptide hormone found on many cells of neuroendocrine origin that acts as a neurotransmitter in the central nervous system (1). Somatostatin receptors have been shown on the surface of human tumor cells, which includes the cells with amine precursor uptake and decarboxylation properties, such as pituitary tumors, endocrine pancreatic tumors, carcinoids, paragangliomas, small-cell lung cancers, medullary thyroid carcinomas, and pheochromocytomas (2, 3). Analogues of somatostatin were developed because human somatostatin has a very short half-life in circulation (2-3 minutes) and is easily broken down by endogenous peptidases (4). These analogues preserved two important molecular features of somatostatin (i.e., its cyclic form and the four amino acids involved in the binding to the receptor). One somatostatin analogue that has been extensively studied in vitro and in vivo is octreotide, which has been used as a hormonal treatment in patients with carcinoid syndrome (5–7). The presence of somatostatin receptors has been used to detect and localize carcinoid, islet cell tumors (8), and small-cell lung cancer (9).

Despite good imaging and diagnostic results with \(^{111}\)In-labeled [DTPA\(^0\)]octreotide (Octreoscan) in the last few years, there have been several reports describing new somatostatin radioligands for studying somatostatin receptor expression. Some, like [DOTA\(^0\), Tyr\(^3\)]octreotide (DOTATOC) labeled with \(^{131}\)I, \(^{90}\)Y, and \(^{177}\)Lu, are also being evaluated for use in the radionuclide therapy of tumors (10). The new peptide receptor radialnuclide therapy (PRRT) using radiolabeled DOTATOC...
has led to tumor responses in the majority of patients but has also posed problems with renal and hematologic toxicities (10). In previous studies, kidney failures have been reported after treatment with DOTATOC labeled to the β-particle emitter 90Y (11–13). In previous clinical studies, it was observed that 10% to 34% patients had complete remission following 90Y-DOTATOC treatment (14). The results of these studies illustrate the partial treatment potentials of this agent and the possible higher relapse rates that may occur in the future (15). The primary challenges that 90Y- or 177Lu-labeled DOTATOC faces are renal toxicities and incomplete treatments, especially in radioreistant tumors. One solution is to use a high linear energy transfer (LET) α-emitter. Several α-emitters have been considered and proposed for this purpose, including 211At. That was recently evaluated for targeting somatostatin receptor—expressing D341 Med human medulloblastoma s.c. xenografts in a murine model (16). 211At is attractive due to its short half-life (7.2 hours), but has notable limitations due to a daughter, 207Bi, which has a long half-life (38 years) and a β-emitting decay product, 207Pb. Further, 211At requires onsite cyclotron production and target processing facilities. Some years ago, 213Bi was proposed for α-immunotherapy (17, 18). It can be readily obtained from a 225Ac/213Bi radionuclide generator system (19). 213Bi decays mainly by β-emission (98%), with a 440 keV γ-emission and a half life ($t_{1/2}$) of 45.6 minutes to the ultra-short-lived high-energy α-emitter 213Po (8375 MeV, $t_{1/2} = 4.2$ μs). 213Bi also has a direct decay pathway by α-emission (2%), 5.87 MeV to the β-particle emitter 209Pb (3.98 MeV; ref. 20). More detailed information of the decay scheme is shown in Fig. 1.

Several studies have shown the successful use of high-LET α-emitters for targeted radionuclide therapy, suggesting their superiority over low-LET β-emitters in the treatment of solid tumors (21, 22). In this study, we aim to evaluate the quantitative radionuclide methods, stability, biodistribution, safety, and therapeutic efficacy of 213Bi labeled to DOTATOC in the treatment of somatostatin receptor—expressing pancreatic tumors.

Materials and Methods

Radioisotope

The 211Bi used in these procedures was obtained from a 225Ac/213Bi radionuclide generator system (NIH, National Cancer Institute, Bethesda, MD; ref. 23). Before each elution, the 225Ac generator column was first rinsed with distilled water and then flushed with air to remove the water. To selectively elute the 211Bi daughter, the column was eluted with 10 mL of 0.1 mol/L hydrochloric acid. The eluate was diluted with water at 5.6 times the eluate volume of water (56 mL). This dilution was loaded onto a MP-50 cation-exchange column. This column was then reverse eluted with an additional 0.4 mL of freshly prepared 0.1 mol/L hydroiodic acid that contained the desired 213Bi (23).

Radio labeling and serum stability

Freshly eluted 213Bi (4 MBq) was added to 0.5 μg of DOTATOC solution and incubated for 5 minutes at 100°C in a hot block. Before heating, the pH of the final solution was adjusted to 6 to 7 using 3 mol/L NH4OAc solution. The specific activity of 213Bi-DOTATOC was 7.4 MBq/μg for all experiments.

Incorporation yield was assessed using Silica Gel instant TLC (ITLC) with 0.9% sodium chloride as the mobile phase. The radiolabeled samples were diluted with 4 mmol/L diethylenetriaminepentaacetic acid (DTPA) at pH 4.1. Five microliters of the diluted sample were spotted on an ITLC silica gel strip and allowed to develop in a chromatography chamber. Upon completion of the migration to the solvent front, the ITLC sample strips were allowed to dry, cut in half, and counted on a Wallac Wizard γ-counter (Perkin-Elmer, Boston, MA) to determine the incorporation yield. Radiochemical purity was assessed via high-performance liquid chromatography (HPLC) analysis. The liquid chromatography system (Thermo Separation Products, San Jose, CA) consisted of a multisolvent delivery pump, an autosampler; a radiometric detector (γ-RAM, IN/US Systems, Inc., Tampa, FL); and a C18, 5 μm, 4.6 × 250 mm, reverse-phase HPLC column. The mobile phase consisted of buffer A [0.5 mol/L ammonium acetate in HPLC grade water (pH 5.5)] and buffer B (100% HPLC grade methanol). The HPLC samples were analyzed with a 1:10 dilution in 4 mmol/L DTPA. The flow rate was 1.0 mL/min and the retention time for the radiolabeled product was 14.0 to 14.5 minutes. The radiolabeled product, 213Bi-DOTATOC, was incubated at 37°C in a CO2 incubator for 24 hours in rat serum obtained from a male Lewis rat to study in vitro stability. After incubation, the product was analyzed by the ITLC and HPLC methods previously described.

Animal model

Lewis rats with and without CA20948 tumor were used for the biodistribution and therapeutic efficacy studies. The tumor model was developed by first injecting somatostatin receptor—positive pancreatic adenocarcinoma cells (CA20948, received from Department of Nuclear Medicine, Erasmus Medical Center, Rotterdam, the Netherlands) into the portal vein of a male Lewis rat. The tumor was allowed to grow in the liver for 14 days. On the 14th day, the animal was sacrificed and the liver was surgically removed. It was then pressed through a sterile screen where it was made into a homogenous solution with sterile PBS by carefully mixing the solution in a sterile pipette to obtain a uniform suspension. This solution was then injected into the right flank of several male rats. Tumor cells were then passaged from rat to rat by injecting 104 tumor cells into the right flank. After 5 to 12 days, the tumor developed in the right flank. Tumor volume estimates were made following caliper measurement of the maximum tumor dimension.

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**Fig. 1.** Decay scheme of 225Ac and 213Bi showing the complexity of the isotopes, their half lives, decay modes, branching fractions, and maximum energies.
Biodistribution studies

Eighteen rats, 15 of them non–tumor bearing, were given a single i.v. injection (penile vein) of unlabeled free $^{213}$Bi radionuclide, $^{213}$Bi-DOTATOC, or unlabeled DOTATOC (blocking dose) coadministered with $^{213}$Bi-DOTATOC. The animals were sacrificed 1 and 3 hours postinjection at which time the pancreas, adrenals, pituitary, stomach, spleen, liver, testes, bone marrow, blood, muscle, bladder, and kidneys were harvested to determine the biodistribution characteristics of the drug. Due to the extremely short half-life of this isotope, the 3-hour rats were given a larger dose of the radiolabeled peptide. The non–tumor-bearing rats were given $6.5 \pm 0.33 \text{ MBq}$ for the 1-hour time point and $12.9 \pm 1.08 \text{ MBq}$ or the 3-hour time point, whereas the tumor-bearing rats were given $9.3 \pm 2 \text{ MBq}$ for the 1-hour time point. The blocking dose was 250 $\mu$G DOTATOC. The obtained organ samples were weighed and the corresponding localized radioactivity was measured using a $\gamma$-counter. $\gamma$-Counter sensitivity and efficiency was determined by counting five standards prepared by geometric dilutions of the injectate. The percentage injected dose per gram of tissue per organ was calculated by comparison with the total injected dose per animal.

Cancer treatment studies and toxicology

Acute toxicity study. Acute toxicity was assessed at 25 days in four groups of tumor-bearing male Lewis rats (average volume $0.75 \pm 0.3 \text{ mm}^3$). Cohort 1 ($n = 4$) served as the control group and was injected twice daily with unlabeled DOTATOC on 3 consecutive days. Rats in the first treatment group, cohort 2, were injected on day 1 only. Rats in cohort 3 were injected on days 1 and 2, whereas rats in cohort 4 were injected on days 1, 2, and 3. Rats were injected with 2.56, 0.5, and 0.5 $\mu$G DOTATOC on days 1, 2, and 3, respectively, with a nominal activity of 3.7 MBq. Each dose was divided into two injections at 1-hour intervals. The rats received the following cumulative average activities per group: cohort 2 ($n = 3$) received $4.3 \pm 0.7 \text{ MBq}$, cohort 3 ($n = 3$) received $9.0 \pm 0.4 \text{ MBq}$, and cohort 4 ($n = 4$) received $12.6 \pm 0.3 \text{ MBq}$ of $^{213}$Bi-DOTATOC.

After 24 days, the animals were put into metabolic cages to collect urine samples for creatinine clearance analysis. Creatinine clearance was determined as previously described (24). After 24-hour urine collection, the animals were euthanized with halothane. For blood collection, a urine sample was obtained from the animals and the animals were euthanized. For blood collection, a cardiac puncture was done. Blood analysis consisted of hemoglobin, hematocrit, RBC, WBC with differential, and platelets. Serum T4 and T3 were determined. Due to the extremely short half-life of this isotope, the 3-hour rats were injected twice daily with unlabeled DOTATOC on 3 consecutive days. Rats in the first treatment group, cohort 2, were injected on day 1 only. Rats in cohort 3 were injected on days 1 and 2, whereas rats in cohort 4 were injected on days 1, 2, and 3. Rats were injected with 2.56, 0.5, and 0.5 $\mu$G DOTATOC on days 1, 2, and 3, respectively, with a nominal activity of 3.7 MBq. Each dose was divided into two injections at 1-hour intervals. The rats received the following cumulative average activities per group: cohort 2 ($n = 3$) received $4.3 \pm 0.7 \text{ MBq}$, cohort 3 ($n = 3$) received $9.0 \pm 0.4 \text{ MBq}$, and cohort 4 ($n = 4$) received $12.6 \pm 0.3 \text{ MBq}$ of $^{213}$Bi-DOTATOC.

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Additional groups were then designed to study the effects of the treatment on a somatostatin receptor–positive tumor. The first group was designed to study the effects of treatment on large volume tumors (average volume $1.720 \pm 608 \text{ mm}^3$). This group, cohort 5 ($n = 5$), received three fractionated doses of $^{213}$Bi-DOTATOC with a total average cumulative dose of $13.0 \pm 0.5 \text{ MBq}$ of $^{213}$Bi-DOTATOC. Another cohort, cohort 6 ($n = 4$), was injected with two fractionated doses of $^{213}$Bi-DOTATOC with a total average cumulative dose of $22.2 \pm 0.7 \text{ MBq}$ of $^{213}$Bi-DOTATOC. As described earlier, each dose was divided into two injections separated by a 1-hour interval. Tumor response to the treatment was assessed in all cohorts by daily tumor measurements.

A 26-week chronic toxicity study was done in three groups of rats. The first group, cohort 7 ($n = 4$) received three fractionated doses of DOTATOC. The second group, cohort 8 ($n = 3$), received three fractionated doses of $^{213}$Bi-DOTATOC with a total average cumulative dose of $12.75 \pm 1.1 \text{ MBq}$. The third group, cohort 9 ($n = 3$), received D-lysine (concentration 400 mg/kg) 10 to 20 minutes before receiving three fractionated doses of $^{213}$Bi-DOTATOC with a total average cumulative dose of $11.39 \pm 0.14 \text{ MBq}$. Rats were injected with 2.56, 0.5, and 0.5 $\mu$G DOTATOC on days 1, 2, and 3, respectively. As described earlier, each dose was divided into two injections separated by a 1-hour interval.

Pathology. Organs were harvested and immediately placed in 10% formalin for a minimum of 48 hours. Following fixation in formalin, bone samples were placed in decalcifying solution for 36 hours. Trimmer organs were sent to the TriCore Laboratories (Albuquerque, NM) where they were embedded in paraffin, sectioned, and stained with H&E. Histopathologic evaluation was done by a board-certified veterinary pathologist (D.F. Kusewitt) who examined the following organs of each animal: heart, lung, kidneys, testicles, spleen, pancreas, pituitary bone marrow, urinary bladder, adrenals, and two different sections of the liver.

Sections of both the right and left kidneys were examined to determine nephrotoxicity in all cohorts. Bone marrow was examined to evaluate hypoplasia and other lesions in cohorts 3 and 4. Interstitial nephritis and bone marrow were scored as follows: 0, no lesions; 1, minimal lesions; 2, mild lesions; 3, moderate lesions; and 4, severe lesions.

Statistics

For the pathology scoring, to evaluate nephrotoxicity on the six acute and the three chronic treatment groups, frequency analyses were done in StatXact-5 using the Jonckheere-Terpstra Test. For all other data, graphs and calculations were done in Graph Pad Prism-4 using the $t$ test. The results of statistical tests were considered significant when $P < 0.05$. Animal biodistribution and tumor volume data are expressed as the average, plus or minus the SEM.

Results

The radiolabeling incorporation yields and radiochemical purity by ITLC and HPLC were $\geq 99.9\%$ and $> 95\%$, respectively. $^{213}$Bi-DOTATOC was unchanged after 24 hours of in vitro incubation in rat serum demonstrating acceptable stability. Administration of free $^{213}$Bi, compared with $^{213}$Bi-DOTATOC, resulted in higher accumulation of radioactivity in nontumor bearing rats at 3 hours postinjection in the following organs: the kidneys [34.47 $\pm$ 1.40% injected dose/g (ID/g) versus 11.15 $\pm$ 0.46%, $P < 0.0001$], the bone marrow (0.31 $\pm$ 0.01% ID/g versus 0.06 $\pm$ 0.02%, $P < 0.00023$), the spleen (0.36 $\pm$ 0.02% ID/g versus 0.08 $\pm$ 0.01%, $P < 0.0053$), the liver (0.50 $\pm$ 0.05% ID/g versus 0.14 $\pm$ 0.02%, $P < 0.002$), the blood (0.07 $\pm$ 0.01% ID/g versus 0.02 $\pm$ 0.00%, $P < 0.022$), the testis (0.03 $\pm$ 0.01% ID/g versus 0.02 $\pm$ 0.00%, $P < 0.16$), and the stomach (0.25 $\pm$ 0.00% ID/g versus 0.08 $\pm$ 0.01%, $P < 0.000015$). The biodistribution data showed receptor specificity to somatostatin receptor–expressing tissues when a blocking dose of DOTATOC was coadministered with the $^{213}$Bi-DOTATOC. The somatostatin receptor–positive organs, pancreas, adrenals, stomach, and pituitary, all showed significantly decreased uptake ($P < 0.05$) of the $^{213}$Bi-DOTATOC following a blocking dose of DOTATOC (Fig. 2A). No significant difference was seen in the receptor-negative organs: blood, liver, spleen, muscle, bone (Fig. 2B), as well as the kidneys, testis, and blood (data not shown). Administration of $^{213}$Bi-DOTATOC in tumor-bearing rats versus non–tumor-bearing rats showed a decreased uptake at 1 hour in the pancreas (3.15 $\pm$ 0.4% ID/g versus 1.44 $\pm$ 0.05%, $P < 0.014$) and the adrenals (3.55 $\pm$ 0.57% ID/g versus 0.50 $\pm$ 0.05%, $P < 0.0061$) as shown in Fig. 3.

Acute toxicity study. No difference in creatinine clearance was seen between the control group (DOTATOC only) and the $^{213}$Bi-treated animals for the 25-day study. Hematology results also did not show any significant differences between the control group and the bismuth-treated animals. No significant changes were found in the follicle-stimulating hormone values.
between treated and control animals. However, significantly lower T4 values were observed in the two highest treatment groups 13.0 MBq (\(P < 0.006\)) and 22.2 MBq (\(P < 0.024\)) compared with control (Fig. 4).

The results of the bone marrow analysis for the DOTATOC control group versus the low dose (12.6 MBq) \(^{213}\text{Bi}\)-DOTATOC treatment group showed no lesions at 25 days; neither hypoplasia nor hyperplasia was observed. The average histopathologic score for nephritis for each treatment group was <1. Representative kidney sections of the treated animals are shown in Fig. 5. Statistical analysis of the data showed that the likelihood of interstitial nephritis increased with increasing dose when all treatment groups were analyzed (\(P < 0.04\) with the Jonckheere-Terpstra test). This significance was lost when the high-dose treatment group (22.2 MBq) was eliminated. Minimal toxicity was seen in the high-dose treatment cohort, except for one kidney in this group, which showed mild interstitial nephritis (Table 1).

Histopathologic examination revealed no evidence of treatment-induced toxicity at 25 days in the heart, lungs, liver, spleen, and urinary bladder. No histopathologic abnormalities were seen in any of the animals in the testes, adrenals, or pancreas. Pituitary cysts were seen in two of four animals in the high-dose (22.2 MBq) treatment group. However, such cysts are generally considered to be incidental findings in Lewis rats (25).

**Chronic toxicity study.** No difference in creatinine clearance was seen between the control group (DOTATOC only) and the bismuth-treated animals for the 26-week study. Hematology results also did not show any significant differences between the control group and the bismuth-treated animals. No significant changes were found in the follicle-stimulating hormone or T4 serum values between treated and control animals.

Histopathologic examination at 26 weeks found minimal nodular cortical hyperplasia in both adrenals in all \(^{213}\text{Bi}\)-DOTATOC–treated rats, whereas only two rats in the \(\beta\)-lysine cohort had one adrenal each with nodular cortical hyperplasia; no adrenal hyperplasia was seen in the control cohort. Microcystic pancreatic degeneration, ranging from mild to moderate, was seen in all of the cohorts. Cardiomyopathy was seen in one rat in the \(^{213}\text{Bi}\)-DOTATOC group, two rats in the \(\beta\)-lysine group, and no rats in the control group. All groups contained some rats with mild to moderate microcystic degeneration in the pituitary. Statistical analysis of the data showed that the likelihood of interstitial nephritis was not significantly different between the control group, \(^{213}\text{Bi}\)-DOTATOC, and \(^{213}\text{Bi}\)-DOTATOC with \(\beta\)-lysine when analyzed with the Jonckheere-Terpstra test (\(P = 0.3147\)). Kidneys had minimal to mild interstitial nephritis (Table 1). All groups showed some mild or moderate cholangiohepatitis and perivasculitis in the liver. Animals in most groups, including the control groups, had minimal to mild interstitial pneumonia.

A significant decrease in the rate of tumor growth was observed at 9 days postinjection in small-volume tumor-bearing
rats (0.75 mm³) treated with low-dose 213Bi-DOTATOC (12.6 MBq) compared with controls (P < 0.037) treated with only nonradioactive DOTATOC (Fig. 6A). In the large-volume tumor-bearing cohorts (1,720 mm³), rats receiving high-dose (22.2 MBq) 213Bi-DOTATOC showed significant tumor reduction (~3×) at 9 days postinjection compared with the rats receiving low-dose treatments (13 MBq; P < 0.025; Fig. 6B).

Discussion

Radionuclide therapy is predominantly based on β-particle emitters, such as 131I, 90Y, or 177Lu. However, a few high-LET α-particle emitters have been evaluated in clinical studies and have shown therapeutic advantages over low-LET radiation emitters in radionuclide therapy (26). It has now been established that radiolabeled peptides can be successfully used in the clinical setting for diagnostic and therapeutic purposes (14). Peptides have the distinct advantages of small molecular weight, excellent permeability, ease of synthesis, and higher-affinity receptor binding compared with other targeted carrier systems, such as monoclonal antibodies. These regulatory peptides are also widely perceived to be comparatively safer than monoclonal antibodies as they generally lack the potential for eliciting an antigenic response (10). It has been previously shown that the short-lived α-particle 213Bi emits 20% of the total α-emissions within 15 minutes after injection, and only 6% of the total α-emissions remain 3 hours postinjection (21). This property of 213Bi makes this cytotoxic radionuclide an attractive candidate for somatostatin receptor–targeted radionuclide therapy as the octreotide-based somatostatin analogues are known to localize in tumor within a few minutes after i.v. injection (27, 28).

As shown in Fig. 2, we have shown that 213Bi-DOTATOC retained its receptor specificity in somatostatin receptor–expressing tissues in normal non–tumor-bearing animals. The somatostatin receptor–positive rat pancreatic tumor (CA20948) model used in this study is well characterized and has been used in numerous similar studies at different centers to evaluate a variety of radiolabeled somatostatin analogues (29–31). The doses of 213Bi-DOTATOC administered for tumor treatment, acute, and chronic toxicity studies were each divided into two injections, separated by a 1-hour interval, to avoid potential mass effects and in consideration of previously established biological half-lives of the octreotide-based somatostatin analogues (27, 30). Tumor growth inhibition was observed in both small- and large-volume tumors following treatment with 12.6 and 22.2 MBq of 213Bi-DOTATOC, respectively. Previous reports indicate that the dose-limiting factor in somatostatin receptor–targeted PRRT is often nephrotoxicity caused by the radiation absorbed dose to the kidneys. The results show only minimal nephrotoxicity at doses ≤13 MBq and mild nephrotoxicity in only one animal was seen with a treatment of 22.2 MBq of
Pancreatic degeneration and nodular cortical hyperplasia, uptake levels resulted in mild to moderate microcystic treatment induced toxicities observed was a slightly lower T4 insights into these observations. The only evidence of other sample sizes and radiation dosimetry are needed to provide Studies of both acute and chronic nephrotoxicity using larger following therapy with the longer-lived, longer-ranged90Y (32).

pared with the moderate to severe nephrotoxicity observed nephrotoxicity caused by short-lived, short-ranged213Bi, com-

pared with the moderate to severe nephrotoxicity observed following therapy with the longer-lived, longer-ranged90Y (32). Studies of both acute and chronic nephrotoxicity using larger sample sizes and radiation dosimetry are needed to provide insights into these observations. The only evidence of other treatment induced toxicities observed was a slightly lower T4 value in the 13 and 22.2 MBq treatment groups at 25 days.

In the chronic 26-week toxicity study, pancreas, and adrenal uptake levels resulted in mild to moderate microcystic pancreatic degeneration and nodular cortical hyperplasia, respectively. The pancreas and adrenal cortex have been shown to express very high density of somatostatin receptor subtype 2 in these animals, much higher than in human tissues, leading to high uptake and retention of somatostatin receptor subtype 2–targeting radiolabeled peptides, such as 213Bi-DOTATOC, within these organs (33). This uptake and retention cause a high radiation absorbed dose to the pancreas and adrenals, probably causing the mild radiotoxic effects as observed. Previous studies of PRRT in humans found the critical organs to be the kidneys and bone marrow whereas no adverse effects were observed in the pancreas and adrenals following administration of somatostatin analogues radiolabeled with various radionuclides (34).

α-Emitting radionuclides, such as 213Bi, offer radiotherapeu-
tic advantages as they emit much higher energy particles than most of the β particles, and yet their ranges are typically two orders of magnitude lower. α-Particles have a high LET that is ~100 times greater than β particles, manifested by a higher relative biological effectiveness and a much shorter range. Consequently, a much greater fraction of the total α-emission energy is imparted to the targeted cancer cell and thus very few nuclear hits are required to kill the cell (35–37). The small path-length cross-kill achievable with 213Bi results in targeted cell killing with only minimal treatment-related toxicities. This further illustrates a strong advantage over 90Y, which conversely has a larger path-length cross-kill, thus significantly increasing toxicity. However, the short-life of 213Bi and the limited availability of the 225Ac/213Bi generator may pose a problem for advanced preclinical and clinical studies. Nevertheless, we believe that 213Bi-DOTATOC may offer an excellent option for the treatment of somatostatin receptor–positive metastatic and hypoxic cancer, which may be difficult to treat with conventional low-LET β-emitters (38). Further studies should also focus on radionuclide therapy combining α-emitting radionuclides, such as 213Bi, with β-emitting radionuclides, such as 90Y or 177Lu, for treatment of solid tumors.

Conclusion

Quantitative radiolabeling of 213Bi to DOTATOC was successfully achieved demonstrating serum stability for ≥24 hours. 213Bi-DOTATOC showed somatostatin receptor–targeted dose-related tumor antiproliferative effects with minimal nephrotoxicity and no other acute or chronic toxicity. 213Bi-DOTATOC is therefore a promising targeted therapeutic radiopharmaceutical for further preclinical evaluation.

Acknowledgments

We thank Dr. Daniel P. Theele for his assistance with animal monitoring throughout the treatment and observation period and Bert F. Bernard for his assistance with tumor biology and animal modeling.

References


213Bi-[DOTA0, Tyr3]Octreotide Peptide Receptor
Radionuclide Therapy of Pancreatic Tumors in a Preclinical Animal Model


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