Glypican-3–Targeted ^{227}Th α-Therapy Reduces Tumor Burden in an Orthotopic Xenograft Murine Model of Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is a significant cause of morbidity and mortality worldwide, with limited therapeutic options for advanced disease. Targeted α-therapy is an emerging class of targeted cancer therapy in which α-particle–emitting radionuclides, such as ^{227}Th, are delivered specifically to cancer tissue. Glypican-3 (GPC3) is a cell surface glycoprotein highly expressed on HCC. In this study, we describe the development and in vivo efficacy of a ^{227}Th-labeled GPC3-targeting antibody conjugate (^{227}Th-octapa-αGPC3) for treatment of HCC in an orthotopic murine model. **Methods:** The chelator *p*-SCN-Bn-H_4octapa-NCS (octapa) was conjugated to a GPC3-targeting antibody (αGPC3) for subsequent ^{227}Th radiolabeling (octapa-αGPC3). Conditions were varied to optimize radiolabeling of ^{227}Th. In vitro stability was evaluated by measuring the percentage of protein-bound ^{227}Th by γ-ray spectroscopy. An orthotopic athymic Nu/J murine model using HepG2-Red-FLuc cells was developed. Biodistribution and blood clearance of ^{227}Th-octapa-αGPC3 were evaluated in tumor-bearing mice. The efficacy of ^{227}Th-octapa-αGPC3 was assessed in tumor-bearing animals with serial measurement of serum α-fetoprotein at 23 d after injection. **Results:** Octapa-conjugated αGPC3 provided up to 70% ^{227}Th labeling yield in 2 h at room temperature. In the presence of ascorbate, at least 97.8% of ^{227}Th was bound to αGPC3-octapa after 14 d in phosphate-buffered saline. In HepG2-Red-FLuc tumor-bearing mice, highly specific GPC3 targeting was observed, with significant ^{227}Th-octapa-αGPC3 accumulation in the tumor over time and minimal accumulation in normal tissue. Twenty-three days after treatment, a significant reduction in tumor burden was observed in mice receiving a 500 kBq/kg dose of ^{227}Th-octapa-αGPC3 by tail-vein injection. No acute off-target toxicity was observed, and no animals died before termination of the study. **Conclusion:** ^{227}Th-octapa-αGPC3 was observed to be stable in vitro; maintain high specificity for GPC3, with favorable biodistribution in vivo; and result in significant antitumor activity without significant acute off-target toxicity in an orthotopic murine model of HCC.

Key Words: hepatocellular carcinoma (HCC); glypican-3 (GPC3); targeted α-therapy (TAT); radioimmunotherapy

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Hepatocellular carcinoma (HCC) is a significant cause of morbidity and mortality worldwide, particularly in advanced stages (*1–3*). Although novel combination therapies are being developed (e.g., immune checkpoint and tyrosine kinase inhibitors), these regimens are limited by modest efficacy and significant adverse effects (*4–7*). New therapies for advanced HCC are needed.

Targeted α-particle therapy is a promising new class of cancer therapies that create double-stranded DNA breaks via a high linear energy transfer and induce a cytotoxic T-lymphocyte–driven antitumor immune response (*8–12*). ^{227}Th (half-life, 18.7 d) is an α-particle–emitting radionuclide that has been attached to monoclonal antibody conjugates using bifunctional octadentate ligands, such as isothiocyanato-benzyl-DOTA and 3,2-hydroxypyridinone derivatives (*13*). The decay scheme of ^{227}Th is shown in Figure 1. α-emitters are appealing for the treatment of solid tumors because of the high radiation payload deposited over short distances (high linear energy transfer), which minimizes the risk of off-target toxicity. ^{227}Th-labeled antibody conjugates are currently being evaluated in the treatment of several malignancies, including acute myeloid leukemia, multiple myeloma, renal cell carcinoma, non-Hodgkin lymphoma, mesothelin-positive mesothelioma, and ovarian cancer (*14–17*). Glypican-3 (GPC3) is a cell surface glycoprotein highly expressed in HCC, making it a promising target for novel therapeutic and diagnostic applications (*18–23*). To our knowledge, no report of ^{227}Th targeted α-particle therapy directed at GPC3 for the treatment of HCC has been published to date.

The objective of this study was to develop a ^{227}Th-labeled GPC3 antibody conjugate (^{227}Th-octapa-αGPC3) and evaluate the radiolabeling properties, in vivo biodistribution, and efficacy in a GPC3-positive hepatic orthotopic xenograft murine model of HCC.

MATERIALS AND METHODS

Conjugation of αGPC3 and αBHV1 with Octapa

$^{227}Th(NO_3)_4$ was purchased from Oak Ridge National Laboratory and was purified from its decay daughters before use (*24*). The bifunctional chelator *p*-SCN-Bn-H_4octapa-NCS (octapa) was synthesized at the University of British Columbia (chemical structure shown in Supplemental Fig. 1; supplemental materials are available at http://jnm.snmjournals.org) (*25,26*). The anti-GPC3 antibody (αGPC3) was generated and

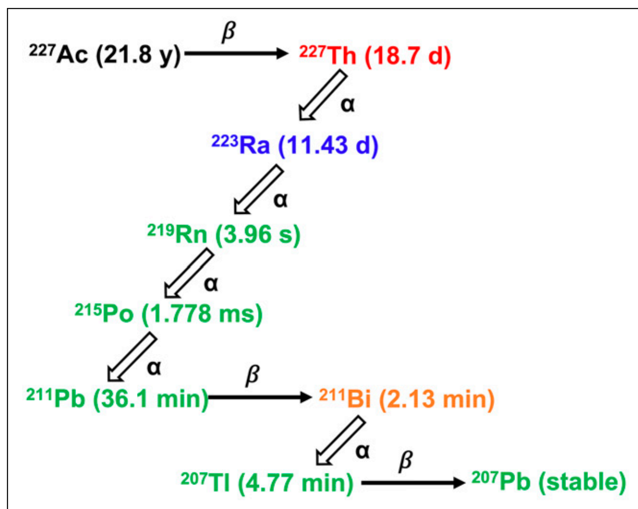

FIGURE 1. Decay scheme of ^{227}Th.

produced at the Fred Hutchinson Research Center antibody core facility as previously described (*22,27*). The isotype control (IgG_1) antibody against bovine herpes virus, αBHV1, was a generous gift from the Orozco laboratory (*28*). The conjugation reaction was previously described (*25,26*). Detailed information regarding conjugation and radiolabeling is included in the supplemental methods.

^{227}Th Radiolabeling of αGPC3-Octapa

The αGPC3-octapa conjugate with the highest octapa-to-αGPC3 ratio and highest antigen binding was used in ^{227}Th-labeling reactions. The radiolabeling yield was optimized by varying the reaction time, pH, and temperature. Appropriate amounts of unlabeled monoclonal antibody conjugates were added to the purified product to provide 18.5 kBq (0.5 μCi) and 70 μg of antibody per dose. The remaining ^{227}Th-labeled αGPC3-octapa was used for in vitro stability studies.

In Vitro Stability of ^{227}Th-Octapa-αGPC3

Solutions of ^{227}Th-labeled monoclonal antibodies were incubated at room temperature and pH 7.0 for 4 h, followed by refrigeration at 4°C, in the presence or absence of ascorbate acid. At 4 h, 24 h, 3 d, 7 d, and 14 d, the percentage of protein-bound ^{227}Th was determined by γ-ray spectroscopy, monitoring the 236-keV (12.9%) γ-peak of ^{227}Th. Stability in serum and in the presence of an excess of metal ions such as Ca^{2+}, Fe^{3+}, Mg^{2+}, Cu^{2+}, and Zn^{2+} will be evaluated in future studies.

Development of Orthotopic Xenograft Model

GPC3-positive HepG2-Red-FLuc cells expressing luciferase were purchased from PerkinElmer (Bioware, catalog number BW134280) and were maintained in a monolayer at 37°C in Dulbecco modified Eagle medium (Gibco) supplemented with 10% fetal bovine serum (Gibco) in a humidified chamber with 5% CO_2.

This study was performed in accordance with the University of Washington Office of Animal Welfare guidelines for the humane use of animals, and all procedures were reviewed and approved by the Institutional Animal Care and Use Committee (protocol 4304-02). Experiments were performed in compliance with the ARRIVE guidelines (Animal Research: Reporting of In Vivo Experiments) (*29*). A hepatic subcapsular xenograft model was generated and described in the supplemental methods (*23*). To monitor orthotopic tumor growth, whole blood was obtained from the animals by a submandibular bleed and the serum concentration of α-fetoprotein (AFP) was determined (*30*).

Biodistribution and Blood Clearance Studies

Tumor-bearing mice were injected with ^{227}Th-octapa-αGPC3 or ^{227}Th-octapa-αBHV1(70 μg, 500 kBq/kg). Tumors and normal organs were harvested and weighed, and ^{227}Th activity was measured by a γ-counter; the measured activity was a net sum of activity from all daughters. The percentage injected dose of radioisotope per gram (%ID/g) of blood, tumor, or organ was calculated after correcting for radioactive decay using an aliquot of the injectate, as were the tumor–to–normal-organ ratios of absorbed radioactivity.

After tumor-bearing mice were injected with ^{227}Th-octapa-αGPC3 or ^{227}Th-octapa-αBHV1 (70 μg, 500 kBq/kg), serial retroorbital blood sampling was performed at 5, 15, 30, 60, 120, and 240 min and then animals were necropsied at 24 h, 7 d, or 23 d after injection. Blood samples were measured by a γ-counter and corrected for ^{227}Th activity.

^{227}Th Radioimmunotherapy

After animals were confirmed to have tumors by IVIS imaging (PerkinElmer), they were included in the study and serum AFP was measured. Tumor-bearing animals were assigned to 1 of 4 experimental groups based on serum AFP measurements to ensure a comparable tumor burden among cohorts. In an unmasked fashion, the animals received either no treatment, αBHV1-octapa radiolabeled with a 500 kBq/kg dose of ^{227}Th, or αGPC3-octapa radiolabeled with a 250 or 500 kBq/kg dose of ^{227}Th via tail-vein injection without anesthesia. Twenty-three days after injection, the animals were euthanized to evaluate for early antitumor effect of ^{227}Th-octapaα-αGPC3. Serum was obtained for AFP measurement, and randomly selected livers were harvested and placed in 10% (w/v) neutral-buffered formalin.

Statistical Analysis

Statistical analysis was performed with Prism (version 8.0.0, GraphPad Software). The D'Agostino and Pearson normality test was performed to determine whether there was a gaussian distribution. Continuous variables were expressed as medians and means and compared by the Student *t* test or Mann–Whitney test. One-way ANOVA or a Kruskal–Wallis test with Dunn multiple comparisons was performed. In all cases, a P value of 0.05 or less was considered statistically significant.

RESULTS

GPC3 Conjugation with Octapa Is Highly Efficient

Octapa was conjugated to αGPC3 via reactions conducted using 5, 10, and 15 equivalents of octapa to determine the optimal conjugation ratio. The isoelectric points of the αGPC3-octapa shifted toward the acidic isoelectric point as the number of equivalents offered increased (Fig. 2). αGPC3-octapa 5 equivalents demonstrated a maximum shift of binding to GPC3-positive cells by flow cytometry (Supplemental Fig. 2); however, it resulted in lower chelates per antibody than did the 10 equivalents. Therefore, a 10-equivalent conjugation ratio was used for subsequent experiments. The protein recovery from the conjugation process was more than 85%, and the final concentrations were 4.6 mg/mL and 4.75 mg/mL for αGPC3-octapa and αBHV1-octapa, respectively. Mass spectral analysis of αGPC3-octapa and αBHV1-octapa conjugates produced by reaction of 10 equivalents of octapa indicated that there was an average of 3.3 octapa moieties on αGPC3 and 5 octapa moieties on αBHV1.

^{227}Th-Labeled αGPC3-Octapa Is Stable In Vitro

Labeling conditions were optimized using αGPC3-octapa and small quantities of ^{227}Th in 0.1 M HNO_3 (85.1–314.5 kBq, or 2.3–8.5 μCi). The labeling yield increased from 16% to 25% to 37% as the reaction time increased from 30 min to 1 h to 2 h, respectively, but did not significantly increase after 2 h. Among the different reaction solutions

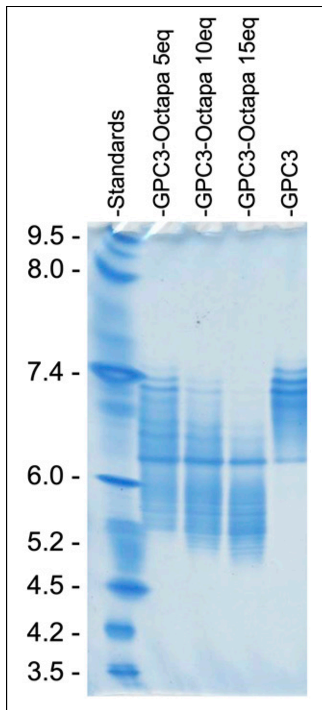

FIGURE 2. Conjugation with octapa to αGPC3: stained isoelectric focusing gel showing isoelectric point changes in unconjugated GPC3 mAb (right lane), when 5, 10, and 15 equivalents of octapa reagent are reacted with αGPC3 mAb.

and pH levels tested, the highest consistent yields were obtained when 200 μL of 0.05 M sodium citrate with 1 mM ethylenediaminetetraacetic acid (pH 5.5) was combined with 5–10 μL of ^{227}Th in 0.1 M HNO_3 with the pH adjusted to 5–5.5 using 1 M sodium citrate. To this, 200 μg of αGPC3-octapa (4.0 mg/mL) were added and allowed to react for 2 h at 37°C (43%–70% radiochemical yield). Reactions conducted at the elevated temperature accounted for only about 4% higher yields; therefore, subsequent reactions were conducted at room temperature.

The in vitro stability of the ^{227}Th-labeled monoclonal antibody–octapa conjugates was evaluated with and without ascorbic acid. Because the γ-counter cannot distinguish ^{227}Th activity from its radioactive progeny, γ-spectroscopy was used to analyze radio–instant thin-layer chromatography strips from, and determine the percentage of antibody-bound, ^{227}Th. After 14 d, at least 97.8% of ^{227}Th was observed to be bound to αGPC3-octapa in the presence of ascorbic acid (Fig. 3).

αGPC3-Octapa Maintains Ligand Binding In Vitro and In Vivo

The affinity of αGPC3-octapa for GPC3 was assessed with flow cytometry using HepG2-Red-FLuc cells. αGPC3-octapa maintained high affinity for GPC3, with only a modest reduction in binding affinity compared with unconjugated αGPC3 (Fig. 4). In tumor-bearing mice 24 h, 7 d, and 23 d after tail-vein injection of ^{227}Th-octapa-αGPC3, elevated levels of radioactivity were detected in the tumor tissue compared with the surrounding liver and other organs (Fig. 5A; Supplemental Table 1). The %ID/g of ^{227}Th-octapa-αGPC3 remained high in tumor tissue over 23 d (Fig. 5B). The %ID/g ratio of ^{227}Th-octapa-αGPC3 in tumor tissue compared with adjacent normal liver parenchyma steadily increased over time (Fig. 5C). ^{227}Th-octapa-αBHV1, an irrelevant isotype antibody conjugate, did not significantly bind to the tumor tissue (Supplemental Fig. 3).

^{227}Th-octapa-αGPC3 did not significantly accumulate in normal tissues at 1, 7, and 23 d after injection (Fig. 5A). The %ID/g of ^{227}Th-octapa-αGPC3 was less than 5% in all tested normal tissues by day 23 after injection. The primary mode of decay for ^{227}Th is α-decay, resulting in daughter ^{223}Ra particles, a radionuclide that preferentially accumulates in bone. Measurement of radioactivity of the femur demonstrated low γ-counts after injection with ^{227}Th-octapa-αGPC3 compared with ^{227}Th-octapa-αBHV1, for which radioactivity was observed to accumulate in bone over time. This observation is presumably due to the highly specific targeting and preferential accumulation of ^{227}Th-octapa-αGPC3 in the tumor, resulting in lower circulating radioactivity for bone deposition. High-resolution γ-ray spectroscopy was performed on select tissues demonstrating radium accumulation in bone (Supplemental Table 2), but further evaluation will be part of a future study.

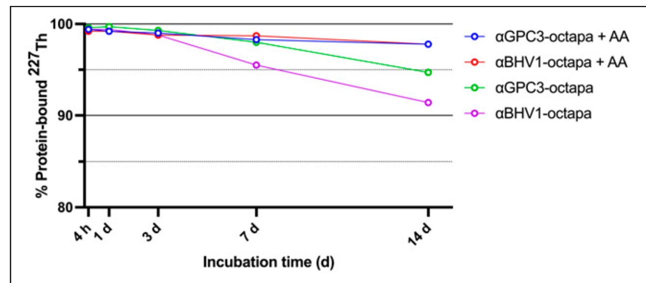

FIGURE 3. Stability of ^{227}Th-labeled mAbs in vitro: percentage bound thorium of αBHV1-octapa and αGPC3-octapa incubated in phosphate-buffered saline over 14 d with and without ascorbic acid (AA).

Blood radioactivity cleared more rapidly after ^{227}Th-octapa-αGPC3 injection than after ^{227}Th-octapa-αBHV1, with serum half-lives of 14 and 17 h, respectively. This more rapid clearance may be secondary to increased accumulation of the radioimmunoconjugate in the tumor over time (Fig. 6).

^{227}Th-Octapa-αGPC3 Reduces Tumor Burden in Murine Model

To assess the efficacy, tumor-bearing mice received either no treatment, a 500 kBq/kg dose of ^{227}Th-octapa-αBHV1, or a 250 or 500 kBq/kg dose of ^{227}Th-octapa-αGPC3 by tail-vein injection. Serum AFP was significantly lower in mice treated with ^{227}Th-octapa-αGPC3 than in control groups 23 d after therapy administration (Fig. 7). The treatment effect was most pronounced after therapy with a 500 kBq/kg dose of ^{227}Th-octapa-αGPC3, although a modest effect was observed after therapy with 250 kBq/kg. AFP increased significantly after therapy with a 500 kBq/kg dose of ^{227}Th-octapa-αBHV1, indicating that

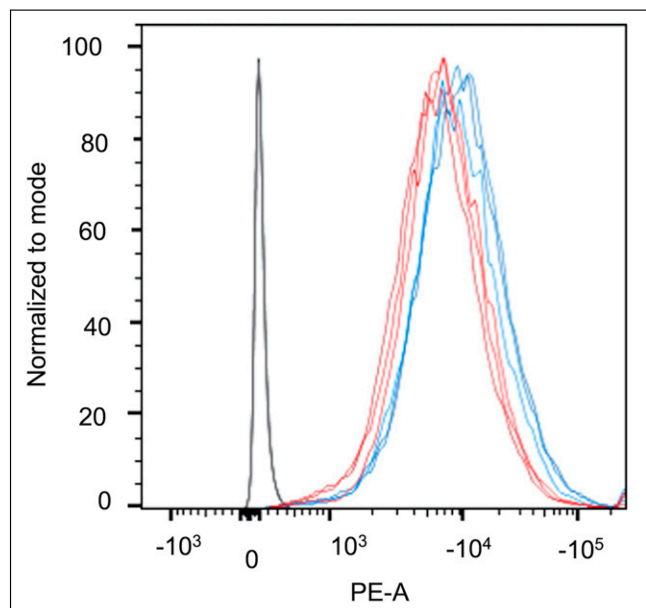

FIGURE 4. Binding affinity for GPC3 in vitro maintained by αGPC3-octapa: in vitro GPC3 binding assessed by flow cytometry on human HepG2-Red-FLuc cells with unconjugated αGPC3 (blue) and αGPC3-octapa (red), compared with unstained control (black). Three biologic replicate samples are shown.

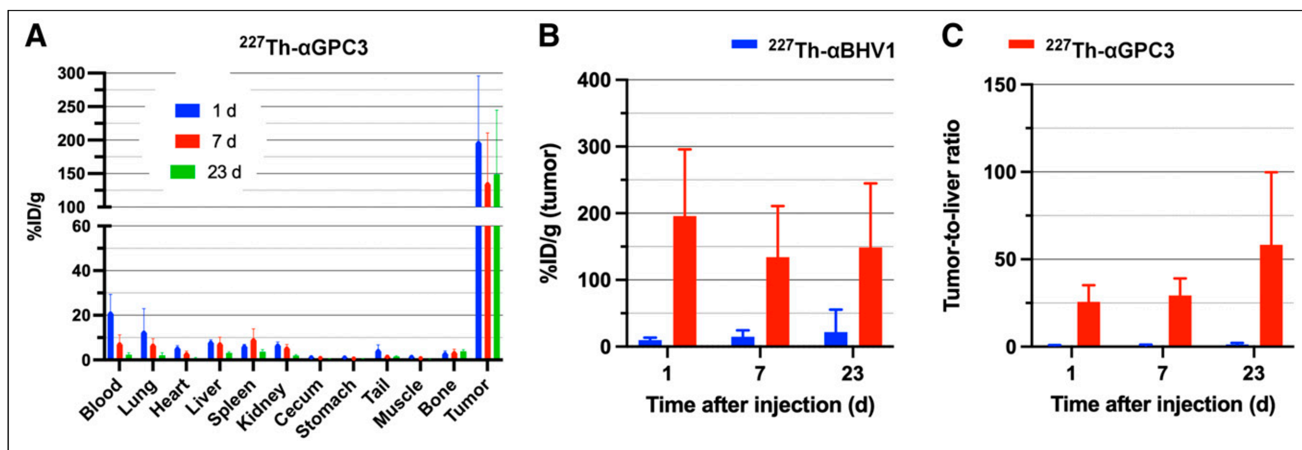

FIGURE 5. Comparative biodistribution of ^{227}Th-octapa-αGPC3 and ^{227}Th-octapa-αBHV1. (A) Tissue biodistribution of ^{227}Th-octapa-αGPC3 in tumor-bearing mice 1 d (n = 7), 7 d (n = 7), and 23 d (n = 6) after injection. (B) ^{227}Th accumulation in tumor tissue. (C) Tumor-to-liver ratio 1 d (n = 7), 7 d (n = 5 for αBHV1 and 3 for αGPC3), and 23 d (n = 4) after injection with ^{227}Th-octapa-αBHV1 or ^{227}Th-octapa-αGPC3. Bar denotes mean; error bar denotes SD.

GPC3-targeted thorium delivery induced tumor cell killing rather than the presence of systemically circulating antibody-bound ^{227}Th.

To assess for organ-specific toxicity after administration of the ^{227}Th radioimmunoconjugates, serum markers of end organ dysfunction were collected 23 d after injection, and no significant aberrations were identified in comparison to controls (Supplemental Fig. 4). No animals died before termination of the study.

DISCUSSION

In this report, we describe the development of a ^{227}Th radioimmunoconjugate targeting GPC3 and demonstrated its in vivo efficacy in the treatment of HCC in an orthotopic murine xenograft model. The ^{227}Th-octapa-αGPC3 radioimmunoconjugate was observed to be stable in vitro; maintain its specificity for GPC3, with a favorable biodistribution; and result in tumor reduction without undesired significant acute toxicity. These findings add to previous studies establishing the basis for a

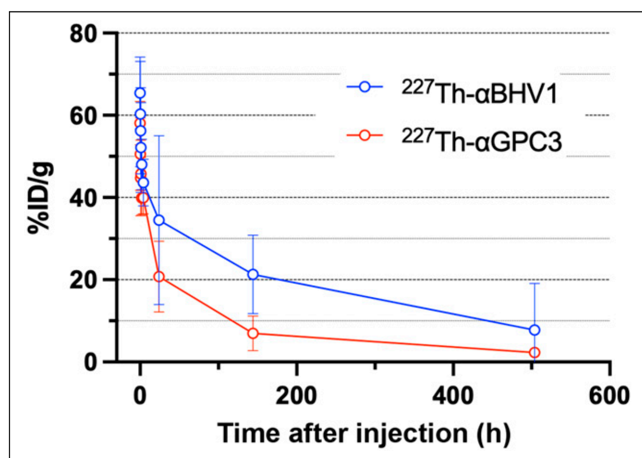

FIGURE 6. Comparative blood clearance profiles in tumor-bearing mice at 5, 15, 30, 60, 120, and 240 min; 24 h; and 7 and 23 d after injection with ^{227}Th-radiolabeled αGPC3-octapa and αBHV1-octapa (n = 4/time point). Symbol denotes mean; error bar denotes SD.

GPC3-targeted theranostic platform whereby different radioimmunoconjugates can be used for diagnostic or surveillance imaging and treatment (*22,23,31,32*). Such a platform could improve current treatments of HCC by enabling earlier identification of disease or recurrence, increase the accuracy of staging, and allow for more targeted treatment with fewer systemic toxicities.

To radiolabel our antibody, we used a picolinic acid–containing chelate, octapa, an octadentate acyclic ligand that enables ^{227}Th radiolabeling of antibodies at room temperature, helping to maintain the 3-dimensional conformation and immunoreactivity of the conjugated targeting antibody (*25,26*). Optimization of the reaction conditions resulted in efficient ^{227}Th-labeling (≤70% radiolabeling yield) and a product with high radiochemical purity. The high in vivo stability of the ^{227}Th-octapa complex is demonstrated by the low bone uptake throughout the 23-d study. In its initial description, H_4octapa was used to label trastuzumab with ^{111}In and ^{177}Lu for imaging and therapy, respectively, of mice bearing ovarian cancer xenografts (*25,26*). Previously ^{227}Th has been radiolabeled to antibodies using an octadentate hydroxypyridinone for the treatment of CD33-positive myeloid leukemia, CD70-positive renal cell carcinoma, and mesothelin-positive malignancies (*13*). To our knowledge, this study is the first to describe picolinic acid ligands as a new class of ligand for ^{227}Th radiolabeling of antibody conjugates.

We have previously described conjugating GPC3 with DOTA chelate for ^{90}Y radioimmunotherapy (*22,23,33*). ^{90}Y produces β-ionizing radiation, with lower energy and a longer pathlength than for ^{227}Th. These differences in properties are important, as a higher energy transfer results in a lower median lethal dose, and a shorter pathlength decreases the radius of tissues affected by the radiation (*10*). α-therapies might be desirable over β-therapies if highly specific targeting is possible. Although research into targeted α-particle therapy for hematologic malignancies has focused on ^{211}At (half-life, 7.21 h), and a recent study for HCC described using ^{225}Ac (half-life, 9.92 d), we elected to use ^{227}Th (half-life, 18.7 d) for its longer half-life, which we hypothesize is advantageous in the treatment of solid tumors (*31,34,35*).

Administration of ^{227}Th-octapa-αGPC3 led to highly specific tumor uptake, rapid blood clearance, and robust antitumor activity without significant acute toxicity. Within 1 d of injection of ^{227}Th-octapa-αGPC3,

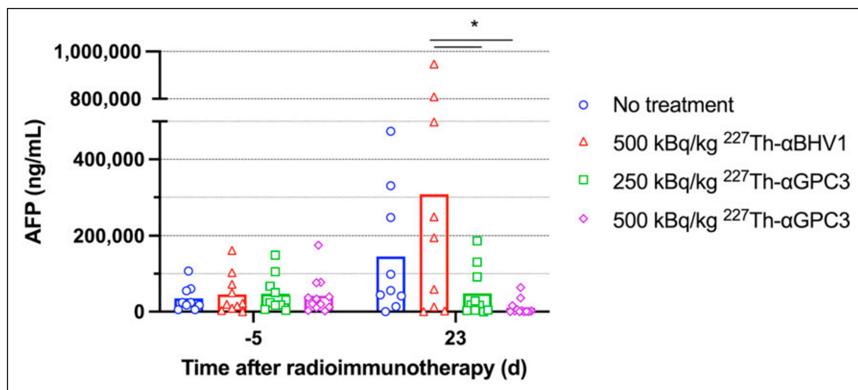

FIGURE 7. Reduction of tumor burden in murine model by ^{227}Th-octapa-αGPC3: serum AFP before (day −5) and 23 d after receiving no treatment (n = 9) or tail-vein injection of 500 kBq/kg dose of ^{227}Th-octapa-αBHV1 (n = 9) or 250 kBq/kg (n = 10) or 500 kBq/kg dose of ^{227}Th-octapa-αGPC3 (n = 12). Bar represents mean. Symbols denote individual mice. *$P < 0.05$ after unpaired 2-way ANOVA with Sidak multiple-comparison test.

significant intratumoral accumulation was observed, compared with controls. The tumor-to-liver ratio of ^{227}Th-octapa-αGPC3 steadily increased over time, and minimal off-target uptake was observed, indicating highly specific targeting and clearance. We observed modest bone uptake over time in the irrelevant isotype antibody control group, which is expected given that ^{227}Th daughter molecule ^{223}Ra delivers radiation to sites of increased osteoblastic metabolism (*36*).

The observed therapeutic effect of ^{227}Th-octapa-αGPC3 was dependent on antibody-targeted delivery of radiation, as evidenced by the lack of therapeutic effect observed in the nontargeting ^{227}Th-octapa-αBHV1 control group. Using an established marker of tumor burden in our model, serum AFP, we observed the therapeutic effect after treatment with a 500 kBq/kg dose of ^{227}Th-αGPC3 to be consistent, with a reduction in serum AFP in all animals except one (*23*). Interestingly, we observed a marked increase in tumor burden in the αBHV1 control group. The mechanism of this finding is not understood but could be related to bone marrow toxicity and suppression of alloreactive immune cells, which are present in athymic mice (*37,38*).

No significant acute off-target toxicity was observed in our study, with all animals surviving until study completion. There was a moderate amount of radioactivity identified in the bone, particularly in our control group. One of the challenges of using α-particle emitters for therapy is the presence of multiple radioactive daughter products that may dislocate from the target site. Although this may lead to cytopenias and marrow toxicity, data from human trials with similar radioisotopes are reassuring. In the phase 3 ALSYMPACA trial, differences in cytopenia rates were seen in patients with prior docetaxel dosing, suggesting that differences in cumulative marrow damage are more implicated than direct radioactive effects. A recently published article describing αGPC3-targeted α-particle therapy using ^{225}Ac conjugated to the humanized monoclonal antibody GC33 in a heterotopic murine xenograft model demonstrated modest antitumor activity while observing significant bone marrow suppression and toxicity (*31*). Although the experimental models tested were different, we postulate that the difference in toxicity between our studies is due to improved specificity of our antibody, highlighting the importance of effective targeting for delivery of the α-therapy.

There are several limitations to our study. GPC3 expression in HCC is variable and differs with the degree of differentiation (*39*). Human HepG2-Red-FLuc cells demonstrate high expression of GPC3 (*40*) and may not recapitulate low- or intermediate-grade HCC. The studies were performed on athymic mice that lack mature T cells. Although competent leukocytes are present in this model, it does not represent the complex tumor microenvironment of human HCC. We elected to omit a nonradiolabeled antibody conjugate control group because of extensive prior work by our group demonstrating that αGPC3 antibody alone does not lead to a robust antitumor response (*23*). Tumor size was measured indirectly in our model by serum AFP. Direct tumor size measurements via ultrasonography or bioluminescent imaging were not performed because of the environmental health and safety constraints at our core facilities with radioactive animals. Some untreated animals showed a spontaneous reduction in AFP and tumor size without treatment, possibly secondary to an alloreactive response from native immune cells. Although these animals existed in all groups, this observation requires further investigation. More studies are warranted to evaluate the potential toxicity of ^{227}Th-octapa-αGPC3. One of the studies would be to perform a dosimetry analysis to understand the radiation dose from ^{227}Th and its α-emitting decay progenies, especially ^{223}Ra. Additionally, it is worth noting that radiation nephropathy and other toxicities were not able to be fully assessed with only 23 d of monitoring (*41*). A longer period of observation in addition to hematologic analysis, which was not performed because of lack of appropriate experimental equipment, is planned for future investigations.

CONCLUSION

We report the development of a GPC3-targeted ^{227}Th conjugate using octapa and demonstrate it to be stable in vitro; maintain high specificity for GPC3, with favorable biodistribution in vivo; and result in significant antitumor activity without undesirable acute toxicity. To our knowledge, this is the first description of a ^{227}Th radiopharmaceutical targeting GPC3 and is a promising addition to the theranostic approach to treating HCC.

DISCLOSURE

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KEY POINTS

QUESTION: Does GPC3-targeted thorium radionuclide therapy localize intratumorally and reduce tumor burden in a mouse model?

PERTINENT FINDINGS: Thorium was reliably and efficiently labeled to a GPC3-targeting antibody via an octapa chelator. This radioimmunoconjugate maintained affinity for the target antigen in vitro and in vivo. Significant levels of thorium accumulated intratumorally. Orthotopic mice treated with GPC3-directed thorium had significant reductions in their tumor burden compared with control animals.

IMPLICATIONS FOR PATIENT CARE: This study identified a new approach to treating HCC using a personalized and targeted approach against a highly expressed antigen in HCC.

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