original reports

B7H3-Directed Intraperitoneal Radioimmunotherapy With Radioiodinated Omburtamab for Desmoplastic Small Round Cell Tumor and Other Peritoneal Tumors: Results of a Phase I Study

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abstract

PURPOSE Desmoplastic small round cell tumor (DSRCT), a rare sarcoma of adolescents/young adults primarily involving the peritoneum, has a long-term survival of < 20% despite aggressive multimodality treatment. B7H3 is expressed on DSRCT cell surface, providing a target for antibody-based immunotherapy.

PATIENTS AND METHODS In this phase I study, we evaluated the safety, pharmacokinetics, and biodistribution of intraperitoneal (IP) radioimmunotherapy (RIT) with the anti-B7H3 murine monoclonal antibody ^{131}I-omburtamab in patients with DSRCT or other B7H3-expressing tumors involving the peritoneum. After thyroid blockade, patients received ^{131}I-omburtamab as a single IP injection at escalated activities from 1.11 to 3.33/GBq/m^2. A prior tracer dose of IP 74 MBq^{124}I-omburtamab was used for radioimmuno–positron emission tomography imaging. Each injection was followed by IP saline infusion.

RESULTS Fifty-two patients (48, three, and one with DSRCT, peritoneal rhabdomyosarcoma, and Ewing sarcoma, respectively) received IP ^{131}I-omburtamab administered on an outpatient basis. Maximum tolerated dose was not reached; there were no dose-limiting toxicities. Major related adverse events were transient: grade 4 neutropenia (n = 2 patients) and thrombocytopenia (n = 1), and grade 1 (10%) and grade 2 (52%) pain lasting < 2 hours related to saline infusion. Hypothyroidism was not observed, and antidrug antibody was elicited in 5%. Mean (± SD) projected peritoneal residence time was 22.4 ± 7.9 hours. Mean projected absorbed doses for ^{131}I-omburtamab based on ^{124}I-omburtamab dosimetry to normal organs were low and well within tolerable limits. More than 80% ^{131}I remained protein bound in blood 66 hours after RIT. On the basis of peritoneal dose and feasibility for outpatient administration, the recommended phase II activity was established at 2.96 GBq/m^2. Patients with DSRCT receiving standard whole-abdominal radiotherapy after RIT did not experience unexpected toxicity.

CONCLUSION IP RIT ^{131}I-omburtamab was well tolerated with minimal toxicities. Radiation exposure to normal organs was low, making combination therapy with other anticancer therapies feasible.

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ASSOCIATED CONTENT

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Desmoplastic small round cell tumor (DSRCT), a rare neoplasm of adolescents and young adults, typically presents with widespread intra-abdominal tumors usually arising from the peritoneum and rarely from other serosal surfaces.[1] DSRCT is characterized by the presence of the t(11;22)(p13:q12) chromosomal translocation,[2] which leads to an *EWS-WT1* fusion.[3,4] Optimal therapy is not well established: tumors are only moderately chemosensitive, and gross total resection (GTR) of disease, although challenging, is necessary for long-term survival.[5] External-beam whole abdominopelvic radiotherapy (WAP-RT) seems to improve outcomes.[6,7] However, despite aggressive multimodality therapy, reported long-term progression-free survival (PFS) is < 20%,[8,9] with treatment failures resulting primarily from intraperitoneal (IP) recurrences caused by a failure to eradicate microscopic residual disease.[10] Results from experimental approaches such as myeloablative chemotherapy with autologous stem-cell transplantation[11] and hyperthermic IP chemotherapy have been disappointing[12,13] and often associated with

CONTEXT

Key Objective

To determine the safety, pharmacokinetics, and biodistribution of intraperitoneal (IP) radioimmunotherapy (RIT) with anti-B7H3 murine monoclonal antibody ^{131}I-omburtamab in patients with desmoplastic small round cell tumor (DSRCT) or other B7H3-expressing tumors. The absence of an effective therapy and the poor long-term survival among patients with DSRCT and other tumors with peritoneal involvement require the development of novel therapies for these rare tumors.

Knowledge Generated

Fifty-two patients (48, three, and one with DSRCT, peritoneal rhabdomyosarcoma, and Ewing sarcoma, respectively) received IP ^{131}I-omburtamab administered as outpatient therapy. Therapy was well tolerated, and there were no dose-limiting toxicities. ^{124}I-omburtamab-mediated radioimmuno–positron emission tomography permitted the assessment of dosimetry and biodistribution. Recommended phase II activity was established at 2.96 GBq/m^2, and outpatient administration was feasible.

Relevance

Radiation exposure to normal organs was low, making combination therapy of IP RIT with other anticancer therapies feasible.

significant toxicity,[14] warranting consideration of other therapies. Peritoneal involvement is extremely rare in other pediatric solid tumors but has been reported for carcinomas,[15] mesothelioma,[16] germ cell tumors,[17] gliomas,[18] neuroblastoma,[19] melanoma, and rhabdomyosarcoma (RMS)[20] and is often associated with a poor prognosis. Furthermore, curative or palliative treatments for malignant ascites remain major unmet needs.[21]

B7H3, a cell surface glycoprotein antigen related to immune checkpoint molecules, inhibits natural killer cells and T cells[22,23] and regulates tumor cell migration and invasion.[24] Whereas B7H3 transcript is expressed ubiquitously in tumors and normal tissues by quantitative reverse transcription-polymerase chain reaction, B7H3 protein was found only on tumors and not on most normal tissues by both Western blot and immunohistochemistry.[5,25,26] We developed the murine monoclonal immunoglobulin (Ig) G1 antibody omburtamab (previously called 8H9) for clinical use. Omburtamab binds to cell surface B7H3 on most pediatric solid tumors, including 96% of DSRCT[27] and in $>$ 80% of other pediatric malignancies that involve the peritoneum; binding to normal tissues is restricted.[28,29] It has a slow dissociation rate (k_{off}), which is crucial for sustained in vivo drug efficacy.[29,30] Radioiodinated omburtamab targets and suppresses RMS xenografts in mouse models.[31]

Compartmental administration of radioimmunotherapy (RIT) achieves favorable dosimetry and higher tumor-to-nontumor ratios when compared with systemic administration and has the potential to reduce systemic radioisotope-related toxicity.[32] In animal experiments, the IP compartment permits a long peritoneal residence time and incomplete transfer of therapeutic agents into the systemic circulation.[33] Intravenous ^{131}I-omburtamab showed liver uptake despite the low level of hepatic expression (ClinicalTrials.gov NCT00582608), suggesting possible sequestration. In a phase I/II study of intraventricular RIT of CNS and leptomeningeal metastases (ClinicalTrials.gov identifier: NCT00089245), omburtamab labeled with the novel positron-emitting isotope ^{124}I allowed the acquisition of radioimmuno–positron emission tomography (PET) images for detailed biodistribution and pharmacokinetic data in patients.[34] These indicated a favorable radiation dose to the cerebrospinal fluid compartment treated with RIT when compared with blood or other normal tissues.[35] The addition of ^{131}I-omburtamab to a multimodality therapeutic regimen has changed the natural history of neuroblastoma metastatic to the CNS with long-term survival rates of $>$ 50% being achieved in what hitherto was a uniformly lethal disease.[36] ^{124}I-omburtamab is also being investigated as a theranostic agent for disseminated intrapontine glioma via intrapontine injection using convection-enhanced delivery (ClinicalTrials.gov identifier: NCT01502917).[37]

We hypothesized that IP RIT with ^{131}I-omburtamab could achieve favorable dosimetry in the peritoneal compartment, have tolerable systemic toxicity, and enhance local control by targeted delivery of radiation to micrometastases, which are poorly accessible by other treatment modalities. We tested this hypothesis in a phase I study in which we investigated the safety of ^{131}I-omburtamab. We studied pharmacokinetics and biodistribution using the radioimmunoconjugate ^{124}I-omburtamab.

PATIENTS AND METHODS

Patients

Patients with DSRCT with peritoneal involvement, or other refractory or relapsed B7H3-expressing tumors involving the peritoneum with $<$ 20% chance of long-term survival, were eligible. Cell surface expression of B7H3 was confirmed by immunohistochemistry for non-DSRCT tumors using methods described previously.[27] Other salient inclusion criteria

included age > 1 year, ability to comply with radiation safety restrictions, and availability of 2×10^6 CD34+ cryopreserved cells/kg for infusion. Key exclusion criteria included the presence of dense peritoneal adhesions preventing adequate IP distribution and grade ≥ 2 toxicities evaluated by National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0, with the exception of myelosuppression.

Study Design

The protocol was approved by the Memorial Sloan Kettering Institutional Review Board (IRB). Written consent was obtained from patients or guardians before study procedures. After high-dose neoadjuvant chemotherapy, patients underwent debulking surgery and adhesiolysis, followed by insertion of an indwelling IP catheter. In general, if abdominopelvic debulking surgery was not deemed feasible, patients were not offered participation in the trial. Five to 7 days before protocol therapy, oral saturated solution of potassium iodide (5-7 drops orally three times a day) and liothyronine (25-75 μg orally per day) was commenced for thyroid protection and continued for a total of 42 days. Thyroid blockade was confirmed by a subnormal thyroid-stimulating hormone (TSH) level before IP injection. Initially, a 74 MBq tracer activity of ^{124}I-omburtamab was injected IP for dosimetry and pharmacokinetic studies. A single therapeutic dose of ^{131}I-omburtamab (radiolabeled at a specific activity of 0.74-1.11 GBq/mg[31]) was administered IP 3 days later. Each activity of RIT was followed by IP infusion of 1.2 L/m^2 saline to expand the peritoneal cavity and facilitate dispersion of RIT. Patients were premedicated with acetaminophen and diphenhydramine. Institutional radiation safety precautions including lead shielding, patient and caregiver education, and portable radiation detectors for dose-rate monitoring were strictly implemented. Radiation exposure dose to family caregivers was maintained at < 500 mrem in compliance with applicable regulations. Toxicity was monitored clinically at weekly clinic visits and biochemically by CBC and complete chemistry. A standard 3+3 phase I design was implemented for escalation of ^{131}I-omburtamab with a starting activity of 1.11 GBq/m^2. Escalation in increments of 0.37 GBq/m^2 was planned if zero of three or one of six patients at each level experienced dose-limiting toxicity (DLT) for a period of 35 days after ^{131}I-omburtamab. DLTs were defined as any grade ≥ 3 toxicity, with the exception of myelosuppression, fever, rash, and hypotension. Autologous stem-cell rescue was mandated if absolute neutrophil count (ANC) was < 500/μL for three consecutive evaluations 28 to 35 days after IP ^{131}I-omburtamab or at any time for life-threatening infection in the presence of ANC < 500/μL. After the recommended phase II dose was established, an additional 24 patients were treated at that activity but were monitored for toxicity for 14 days or until additional therapy was initiated, whichever was later. Immunogenicity was evaluated by measuring human antimouse antibody (HAMA) titers using a previously described enzyme-linked immunosorbent assay.[34] The protocol schema is outlined in Table 1. For patients with measurable disease, response was assessed between days 24 and 38 using RECIST criteria. After mandated observation was completed, patients received additional therapy at the discretion of their primary physicians. Most patients received WAP-RT after IP RIT. PFS and overall survival (OS) were calculated using Kaplan-Meier methodology from the day of ^{131}I-omburtamab administration and were censored on March 1, 2020.

Pharmacokinetics and Radiation Dosimetry

Blood clearance for ^{124}I-omburtamab or ^{131}I-omburtamab was measured using serial venous blood samples drawn at baseline and approximately 1, 2, 8, 18, 24, 30, 42, 66, 90, and 144 hours after IP injection. Measured aliquots of blood were assayed in duplicate, and activity concentrations were derived as % injected activity/gram. Biologic and effective clearance was derived by fitting time-activity concentration data, with decay corrected to the time of administration, to a biexponential function. Mean blood absorbed dose was calculated by multiplying the blood cumulated activity concentration by ^{124}I or ^{131}I equilibrium dose constant for nonpenetrating radiation. Blood clearance was compared for ^{124}I-omburtamab and

TABLE 1. Treatment Schema

Day	Treatment/Intervention
−7 to +35	Oral liothyronine and potassium iodide for thyroid protection
0	Dosimetric dose of ^{124}I-8H9 IP; blood draw for ^{124}I-8H9 pharmacokinetics; PET scan for ^{124}I-8H9 dosimetry
1-4	Blood draw for ^{124}I-8H9 pharmacokinetics; PET scan for ^{124}I-8H9 dosimetry
3	Therapeutic dose of ^{131}I-8H9 IP
3-7	Blood draw for ^{131}I-8H9 pharmacokinetics; γ camera scan for ^{131}I-8H9 distribution
24-38	Extent of disease evaluation
28-35	CBC; decision regarding stem-cell rescue
35*	Observations period ends; patient can continue therapy

Abbreviations: IP, intraperitoneal; PET, positron emission tomography.

*After the recommended phase II dose was established, an additional 24 patients were treated at that activity but were monitored for toxicity for 14 days or until additional therapy was initiated, whichever was later.

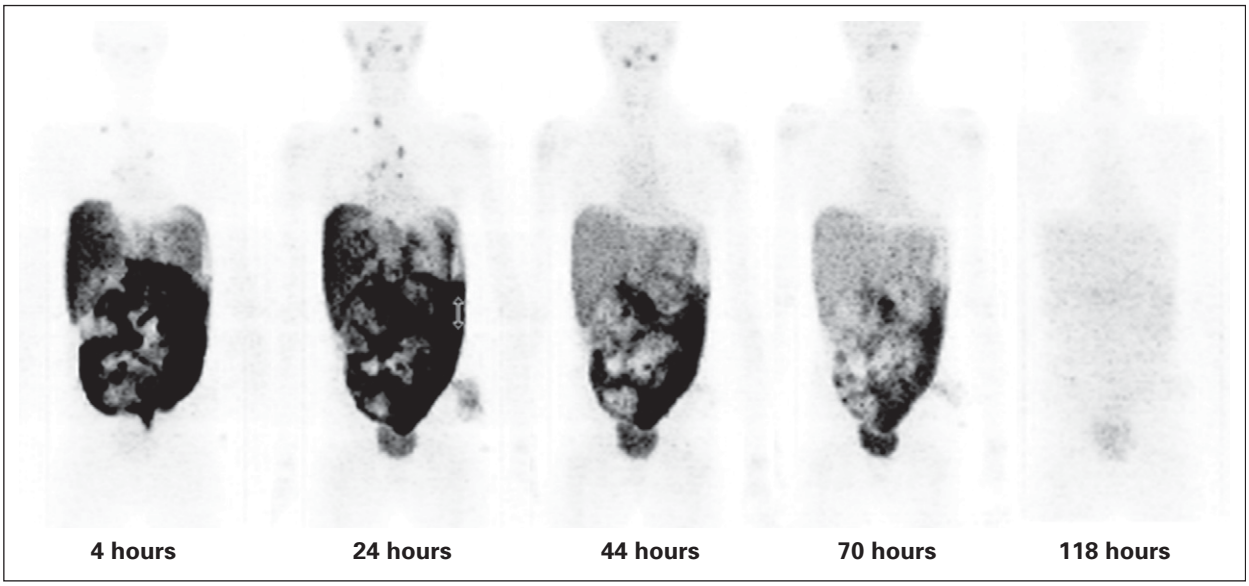

FIG 1. Serial positron emission tomography scans of a study patient, used for organ dosimetry. Numbers indicate hours after IP ^{124}I-omburtamab administration.

^{131}I-omburtamab. In addition, 30 and 66 hours after ^{131}I-omburtamab injection, blood samples were evaluated by trichloroacetic acid precipitation for free radioiodine content.

Whole-body PET scans, using the same scanner and uniform acquisition parameters (Fig 1), were performed within 2 to 4 hours and approximately 24, 48, 120, and 168 hours after ^{124}I-omburtamab injection. Normal organ and whole-body absorbed doses for IP ^{131}I-omburtamab were derived on the basis of ^{124}I-omburtamab imaging using region-of-interest analysis to extract time-activity data of uptake in major organs (heart, liver, spleen, kidneys, GI tract, and peritoneal cavity) and whole body. Cumulated activity concentrations and residence times in each organ were derived. Whole-body clearance, mean organ absorbed doses, effective dose equivalent, and effective dose were calculated using the Organ Level Internal Dose Assessment/EXponential Modeling (OLINDA/EXM) radiation dosimetry program[34] for ^{131}I radionuclide and the Reference Man anatomic model closest in whole-body mass to that of the patient. A peritoneal cavity model was also used.[38] Detailed statistical analysis is described in the Protocol (online only).

TABLE 2. Dose Escalation of ^{131}I-omburtamab

^{131}I-Omburtumab Dose (GBq/m^2)	Planned No. of Patients	Actual No. of Patients Treated
1.11	3	3
1.48	3	3
1.85	3	3
2.22	3-6	7[a]
2.59	3	3
2.96	23	27[a]
3.33	3-6	6
Total		52

[a]Five patients (one at 2.22 GBq/m^2 and four at 2.96 GBq/m^2) were treated on a single-patient–use basis, including four who had pre-existing hypothyroidism and could not be evaluated for thyroid toxicity.

RESULTS

Patient Demographics

Fifty-two patients (41 males and 11 females) received IP RIT with ^{131}I-omburtamab as outpatients (except for the first three patients for whom the IRB required inpatient observation) between 2010 and 2019. These included five patients who were treated on a single-patient use basis: four because they had pre-existing hypothyroidism and could not be evaluated for thyroid toxicity, and one on a compassionate basis after IRB approval. In addition, six enrolled patients could not receive RIT because of blockage of the IP catheter. Forty-eight treated patients had the diagnosis of DSRCT; three and one had B7H3-expressing RMS and Ewing sarcoma, respectively. Median age at RIT was 18.5 years (range, 2.9-38 years), and median time from diagnosis to RIT was 9.9 months (range, 5.1-56.3 months). Median time from catheter insertion to RIT was 17 days (range, 9-32 days). Thirty-five of the 48 patients with DSRCT underwent GTR before RIT; twenty-nine of the 35 without experiencing prior disease progression. Patients with RMS and Ewing sarcoma underwent complete

TABLE 3. ^{131}I-Omburtamab: Related Laboratory Toxicities

^{131}I-Omburtamab Dose (GBq/m^2)	No. Pts	CTCAE Grade											
		Neutropenia				Thrombocytopenia				AST		ALT	
		1	2	3	4	1	2	3	4	1	2	1	2
1.11	3	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (33)	0 (0)	0 (0)	0 (0)
1.48	3	0 (0)	0 (0)	0 (0)	0 (0)	2 (66)	2 (66)	0 (0)	0 (0)	0 (0)	0 (0)	1 (33)	0 (0)
1.85	3	0 (0)	0 (0)	0 (0)	0 (0)	2 (66)	2 (66)	0 (0)	0 (0)	0 (0)	2 (66)	2 (66)	0 (0)
2.22	7	1 (14)	2 (28)	0 (0)	0 (0)	2 (28)	1 (14)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
2.59	3	0 (0)	2 (66)	0 (0)	0 (0)	0 (0)	0 (0)	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
2.96	27	2 (7)	2 (7)	2 (7)	2 (7)	10 (37)	2 (7)	3 (11)	1 (4)	4 (15)	0 (0)	3 (11)	1 (4)
3.33	6	0 (0)	1 (17)	0 (0)	0 (0)	1 (17)	1 (17)	0 (0)	0 (0)	1 (17)	0 (0)	1 (17)	1 (17)
Total	52	4 (8)	7 (13)	2 (4)	2 (4)	17 (33)	4 (8)	4 (8)	1 (2)	6 (12)	2 (4)	7 (13)	2 (4)

NOTE. Data are presented as No. (%).

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; Pts, patients.

cytoreductive surgery before RIT, although all had relapsed previously.

Escalation of ^{131}I-Omburtamab Activity

Initially, the administered activity of ^{131}I-omburtamab was planned to be escalated from 1.11 to 2.22 GBq/m^2/treatment, with six candidates treated at 2.22 GBq/m^2. Because the treatment was well tolerated and no DLT was encountered, ^{131}I-omburtamab administered activity was further escalated to 3.33 GBq/m^2. Again, no DLT was encountered. The recommended phase II activity was established at 2.96 GBq/m^2 (80 mCi/m^2) to allow outpatient administration of ^{131}I-omburtamab while meeting the requirements for the safe administration of radionuclides (typically, 7.4 GBq/dose for ^{131}I). After the recommended phase II activity was established, an additional 24 patients were treated at 2.96 GBq/m^2/dose to acquire further safety data before the opening of a follow-up phase II study. The number of patients treated at each dose level is listed in Table 2. Actual administered activity and protein mass ranged from 1.25 to 7.61 GBq and 1.7 to 10.2 mg, respectively.

Toxicity

Both dosimetry and diagnostic administrations were well tolerated at all dose levels. No DLTs were encountered. Acute toxicities attributable to RIT were related to the large volume of saline flush and were transient (lasting < 2 hours). These included grade 2 pain (52%) and grade 1 (10%) or 2 (10%) vomiting. Two patients experienced grade 1 fatigue lasting < 1 week after IP RIT. Laboratory abnormalities are detailed in Table 3. No intermediate or long-term toxicities attributable to IP RIT were observed. Despite all patients having received high doses of chemotherapy before IP RIT, grade > 2 myelosuppression was uncommon and was encountered only at doses > 2.22 GBq/m^2. Myelosuppressive changes were self-limiting without intervention in general; one patient each required filgrastim (1 dose) and platelet transfusion (single aliquot). No patient required autologous stem cell rescue after RIT. Hypothyroidism, as assessed by TSH measurements after discontinuation of iodine drops and liothyronine, was not seen in any patient (n = 37 of 49 evaluable). HAMA developed in two of 44 tested patients (5%).

Pharmacokinetics and Dosimetry

^{124}I-omburtamab–based dosimetry was studied for the first 33 patients. Blood radiation exposure was low, and pharmacokinetics exhibited a biphasic pattern for both ^{124}I-omburtamab (n = 29) and ^{131}I-omburtamab (n = 36). This consisted of an initial rising phase with a mean (± SD) half-time of 49.6 ± 65.6 hours and a subsequent falling phase with a mean half-time of 70 ± 118.4 hours for ^{124}I-omburtamab. Calculations that included four patients in whom low-level activity persisted in the blood contributed to the wide SD: respective early- and late-phase half-times after discounting these outliers were 27.9 ± 21.2 hours and 49.2 ± 25.9 hours. For ^{131}I-omburtamab, respective early- and late-phase half-times were 17.3 ± 21.5 hours and 69.1 ± 33.4 hours. Using ^{124}I-omburtamab data, calculated median projected blood exposure for ^{131}I-omburtamab was 0.67 ± 0.34 mGy/MBq; this compared well with actual blood exposure for ^{131}I-omburtamab, which was 0.84 ± 0.46 mGy/MBq. In 24 patients, for whom both ^{124}I-omburtamab and ^{131}I-omburtamab kinetics data were available, a positive correlation was observed between estimates for the two groups (r = 0.43). Radioactivity in the circulation was largely blood bound: whole-blood free iodine content at 30 and 66 hours was only 6.9% ± 3.9% and 4.2% ± 3%, respectively (n = 43).

^{124}I-omburtamab–based whole-body and organ dosimetry for ^{131}I-omburtamab (n = 33 patients) is reported in Table 4. Mean whole-body clearance half-time and residence times were 44.4 ± 9.2 hours, and 51.7 ± 8.6 hours, respectively. Peritoneal residence time was 22.4 ± 7.9 hours. In general,

TABLE 4. Mean Organ-Absorbed Doses of ^{131}I-Omburtamab (mGy/MBq) on the Basis of ^{124}I-Omburtamab Dosimetry (n = 33 patients)

	^{131}I-Omburtamab Dose (mGy/MBq)	
Organ	**Mean**	**SD**
Peritoneum	0.65	0.21
Adrenals	0.23	0.04
Brain	0.07	0.04
Breasts	0.08	0.04
Gall bladder wall	0.13	0.05
Lower large intestine wall	0.13	0.04
Small intestine	0.25	0.05
Stomach wall	0.46	0.15
Upper large intestine wall	0.23	0.04
Heart wall	0.24	0.05
Kidneys	0.37	0.10
Liver	0.51	0.19
Lungs	0.11	0.04
Muscle	0.12	0.04
Ovaries	0.21	0.03
Pancreas	0.46	0.12
Red marrow	0.12	0.03
Osteogenic cells	0.20	0.07
Skin	0.07	0.04
Spleen	0.35	0.16
Testes	0.08	0.04
Thymus	0.09	0.04
Thyroid	0.73	2.02
Urinary bladder wall	0.66	0.28
Uterus	0.51	0.06
Whole body	0.13	0.04

radiation exposure to normal organs was low, with the highest projected absorbed doses noted for the thyroid, urinary bladder wall, uterus, liver, pancreas, and stomach wall. The projected absorbed dose to the peritoneum was 0.65 ±0.21 mGy/MBq. Although the total absorbed dose to the peritoneum increased as administered activity was increased, it seemed to plateau at 2.96 GBq/m^2 (Fig 2). Of the 33 patients undergoing dosimetry studies, only one patient had unresected abdominopelvic disease at the time of ^{124}I-omburtamab PET scans. This single gastrohepatic node was visualized on PET at 21 hours after injection and the projected ^{131}I-omburtamab dose was calculated as 0.59 mGy/MBq. γ-single-photon emission computerized tomography (SPECT) scans after IP ^{131}I-omburtamab generally showed good peritoneal distribution for all patients.

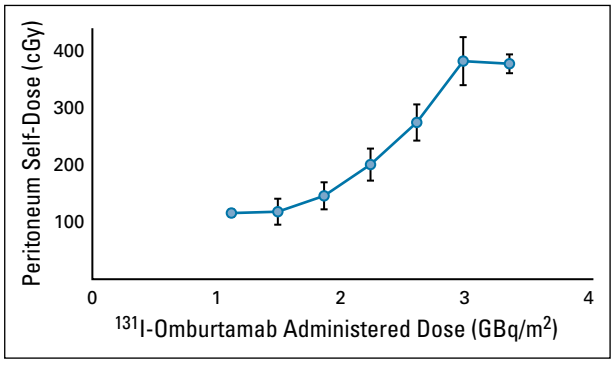

FIG 2. Relation of mean peritoneal absorbed dose to injected activity. Error bars represent SEM.

Responses, Post-RIT Therapy, and Survival in Patients With DSRCT

At study entry, 13 patients had measurable disease before IP RIT, whereas 35 had no evaluable DSRCT. As expected with RIT designed to target micrometastases, no responses were observed in patients with measurable disease. Immediate post-RIT therapy included 3,000 cGy WAP-RT (n = 30) administered at a median of 35 days (range, 16-74 days) after RIT, chemotherapy (n = 12), allogeneic transplantation (n = 3), and no therapy at all (n = 3). Of the 30 patients undergoing WAP-RT, 18 received ASCR after completing WAP-RT, either electively (n = 6) or to reduce the duration of thrombocytopenia to permit additional therapy (n = 12). All patients undergoing stem-cell infusions had hematopoietic reconstitution.

Survival was significantly worse for patients with residual disease receiving IP RIT compared with those treated after R1 resection; median PFS and OS (statistical analysis for survival described in Protocol) for the two groups was 8.6 ± 2.1 months versus 15.2 ± 0.9 months and 16.9 ± 4.3 months versus 54.1 ± 9.2 months, respectively ($P <$ 0.01 for both). Of the 23 patients receiving IP RIT after GTR at the recommended phase II dose or higher, nine remain alive and disease free at a median follow-up of 42 months after RIT, and only four (17%) developed their initial relapse in the abdominopelvic compartment. Patients receiving $<$ 2.96 GBq/m^2 (the recommended phase II dose; n = 12) after GTR had a poorer (although statistically nonsignificant) median abdominal PFS (15 ± 9.1months) than did the 23 who received ≥ 2.96 GBq/m^2 (25.7 ± 6.7 months; P = .2).

Outcome in Patients Without DSRCT

None of the three patients with RMS had measurable disease at the time of IP RIT. Of these, two remain alive without recurrence at ≥ 29.4 and ≥ 97.4 months after RIT. The sole patient with disseminated abdominopelvic Ewing sarcoma had no response to IP RIT and developed rapidly progressive disease.

DISCUSSION

Intracompartmental delivery is an attractive approach for RIT when the targeted disease is restricted mainly to a particular body compartment, as in DSRCT. The

intracompartmental approach is particularly suited to RIT with the murine IgG1 monoclonal antibody omburtamab, which has limited recruitment of human effectors but has a high affinity to the target antigen B7H3. Because B7H3 is also expressed on common malignancies such as carcinomas,[39] ^{131}I-omburtamab–mediated IP RIT has potential in the management of carcinoma-associated malignant ascites, a complication for which there are no established curative or palliative therapies. In this first phase I trial of IP-administered ^{131}I-omburtamab, we established its safety; related toxicities were mild and transient, with the main adverse event being short-lasting abdominal pain and distension related to IP saline infusion after RIT. Myelosuppression was grade < 4 in almost all patients, and only one patient required a blood product (platelet support). Outpatient administration meeting all radiation safety regulatory limits was feasible when activity of 2.96 GBq/m^2 was administered to both children and adults. An additional reason for establishing 2.96 GBq/m^2 as the recommended phase II activity was the plateau in peritoneal dose, a critical factor in effective RIT delivery.

Omburtamab retained binding to ^{131}I after it transitioned from the peritoneum to the blood, with $< 10\%$ free iodine being detected in the blood. This could explain the relatively mild myelosuppression encountered despite patients having previously received high-dose chemotherapy typically administered for DSRCT and high-risk RMS. The lack of hypothyroidism and a low projected thyroid uptake of < 500 rads were remarkable for a radioiodinated antibody, indicating the success of the thyroid blockade regimen. The low incidence of antidrug antibody (HAMA) could be a result of immune suppression mediated by alkylator-containing chemotherapy[5] received by patients before RIT. Low blood and systemic radiation exposures have also been observed in other intracompartmental therapies with radioiodinated omburtamab.[35]

Although other radioimmunoconjugates have been used in the past for IP RIT, primarily to target surface antigens on ovarian carcinoma,[40-42] to our knowledge ours is the first in a predominantly pediatric/adolescent population. Organ biodistribution for other radioimmunoconjugates, because of the choice of radioisotope used (eg, α emitters) or era of trials (predominantly γ emitters), could only be estimated by relatively less precise methods such as γ-SPECT scans[43] or external radiation probes.[44] The availability of the positron-emitting radioimmunoconjugate ^{124}I-omburtamab allowed us to derive precise organ exposures for therapeutic ^{131}I-omburtamab. To our knowledge, this is the first study to use radioimmuno-PET to assess dosimetry and biodistribution for IP RIT. The strong correlation in blood pharmacokinetics between ^{124}I-omburtamab and ^{131}I-omburtamab strengthened the validation of this approach. Calculated organ exposure was well within tolerated limits for all organs, corroborated by the observed lack of toxicities. The calculated radiation dose to the peritoneum was comparable to that reported in the only other IP RIT study reporting on dosimetry in humans.[43] For most patients treated with the proposed phase II activity of ^{131}I-omburtamab, the peritoneal dose was < 500 cGy, although as with other studies, we could not calculate the dose to the tumor because most patients did not have grossly evaluable or measurable disease at study entry or had disease in other body compartments not accessible to IP RIT. The relatively modest whole-peritoneal radiation dose permitted the safe administration of 3,000 cGy whole-abdominal radiotherapy after IP RIT to most patients with DSRCT. Patients with RMS had received WAP-RT before IP RIT and did not experience unforeseen adverse events.

As expected for a therapeutic modality targeted at microscopic or minimal disease, we did not see tumor responses in measurable IP or extraperitoneal disease. Survival evaluation for patients with DSRCT was not the main objective of this phase I study. However, we deemed it important to analyze because we wanted to evaluate the impact of ^{131}I-omburtamab when added to multimodality therapy (high-dose chemotherapy, GTR of tumor, and WAP-RT), which is considered standard-of-care at our institution. Patients receiving IP RIT in addition to standard therapy had superior PFS and OS compared with historical data on patients who received a similar multimodality regimen without IP RIT (median OS of 54 months for the former *v* 36 months for the latter).[10] In addition, two of three patients with recurrent RMS in the peritoneal compartment are long-term relapse-free survivors after receiving WA-IMRT followed by IP RIT. Based on the favorable toxicity profile of ^{131}I-omburtamab and the encouraging preliminary data generated from this phase I trial, we have initiated a phase II trial of IP RIT in patients with DSRCT with ^{131}I-omburtamab as a single dose of 2.96 GBq/m^2 followed 2 to 4 weeks later by WA-IMRT at 3,000 cGy to the whole abdomen, with the goal of improving survival (ClinicalTrials.gov identifier: NCT04022213). Patients with relapsed RMS and other high-risk B7H3-expressing tumors involving the peritoneum will also be eligible. In addition, preclinical testing of ^{177}Lu177-omburtamab, a β-emitting radioimmunoconjugate that might be more conducive to IP RIT, is underway.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

B7H3-Directed Intraperitoneal Radioimmunotherapy With Radioiodinated Omburtamab for Desmoplastic Small Round Cell Tumor and Other Peritoneal Tumors: Results of a Phase I Study

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