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Fractionated Radioimmunotherapy With ^{90}Y-Clivatuzumab Tetraxetan and Low-Dose Gemcitabine Is Active in Advanced Pancreatic Cancer

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Abstract

BACKGROUND—It has been demonstrated that the humanized clivatuzumab tetraxetan (hPAM4) antibody targets pancreatic ductal carcinoma selectively. After a trial of radioimmunotherapy that determined the maximum tolerated dose of single-dose yttrium-90-labeled hPAM4 (^{90}Y-hPAM4) and produced objective responses in patients with advanced pancreatic ductal carcinoma, the authors studied fractionated radioimmunotherapy combined with low-dose gemcitabine in this disease.

METHODS—Thirty-eight previously untreated patients (33 patients with stage IV disease and 5 patients with stage III disease) received gemcitabine 200 mg/m^2 weekly for 4 weeks with ^{90}Y-hPAM4 given weekly in Weeks 2, 3, and 4 (cycle 1), and the same cycle was repeated in 13 patients (cycles 2–4). In the first part of the study, 19 patients received escalating weekly ^{90}Y doses of 6.5 mCi/m^2, 9.0 mCi/m^2, 12.0 mCi/m^2, and 15.0 mCi/m^2. In the second portion, 19 additional patients received weekly doses of 9.0 mCi/m^2 or 12.0 mCi/m^2.

RESULTS—Grade 3/4 thrombocytopenia or neutropenia (according to version 3.0 of the National Cancer Institute's Common Terminology Criteria for Adverse Events) developed in 28 of 38 patients after cycle 1 and in all retreated patients; no grade >3 nonhematologic toxicities occurred. Fractionated dosing of cycle 1 allowed almost twice the radiation dose compared with single-dose radioimmunotherapy. The maximum tolerated dose of ^{90}Y-hPAM4 was 12.0 mCi/m^2 weekly for 3 weeks for cycle 1, with ≤9.0 mCi/m^2 weekly for 3 weeks for subsequent cycles, and that dose will be used in future trials. Six patients (16%) had partial responses according to computed tomography-based Response Evaluation Criteria in Solid Tumors, and 16 patients (42%) had stabilization as their best response (58% disease control). The median overall survival was 7.7 months for all 38 patients, including 11.8 months for those who received repeated cycles (46% [6 of 13 patients] ≥1 year), with improved efficacy at the higher radioimmunotherapy doses.

CONCLUSIONS—Fractionated radioimmunotherapy with ^{90}Y-hPAM4 and low-dose gemcitabine demonstrated promising therapeutic activity and manageable myelosuppression in patients with advanced pancreatic ductal carcinoma.

Keywords

combination therapy; gemcitabine; ductal pancreatic cancer; radioimmunotherapy; clivatuzumab tetraxetan; ^{90}Y

INTRODUCTION

Despite considerable efforts to improve the management of pancreatic ductal cancer (PDC), the only approved treatments for advanced disease offer minimal survival benefit (median survival, approximately 6 months).[1–3] Recently, two multi-drug combinations reportedly improved survival but with substantial toxicities.[4,5] In preclinical models, pancreatic cancer has been responsive to radioimmunotherapy (RAIT) with radiolabeled clivatuzumab tetraxetan (PAM4),[6,7] a monoclonal antibody that specifically targets a mucin antigen that is produced in >85% of pancreatic adenocarcinomas and is absent in normal pancreas.[8–10] Hence, the PAM4 antibody was humanized (hPAM4), and a chelate conjugate was labeled with yttrium-90 (^{90}Y-hPAM4), a therapeutic β-emitting radionuclide with an effective mean radiation path length of approximately 5 mm that is suitable for bulky tumors.

On the basis of clinical experience with external radiotherapy and other studies using ^{90}Y-labeled antibodies,[11] we speculated that fractionated doses could deliver more radiation than a single bolus. Preclinical studies also indicated enhanced antitumor activity when ^{90}Y-hPAM4 was combined with gemcitabine,[12–14] a known radiosensitizer.[15] Clinically, low doses of gemcitabine with external radiotherapy were tolerated.[16] In the first phase 1 trial of single-dose hPAM4 RAIT, the maximum tolerated dose (MTD) was identified as 20 mCi/m^2 (740 megabecquerels [MBq]/m^2), with expected dose-limiting myelotoxicity.[17] Despite receiving only a single administration, several patients had an objective response. Hence, in the current study, we examined fractionated RAIT using ^{90}Y-hPAM4 combined with low-dose gemcitabine in patients with advanced PDC. The overall objective of the study was to determine the MTD of this combination as first-line therapy. With escalating RAIT doses and a constant gemcitabine dose, patients optionally received repeated cycles. Correlative ^{18}F-deoxyglucose–positron emission tomography (FDG-PET) and CA19-9 serum titer changes also were evaluated. The results would determine the dose schedule for future trials.

MATERIALS AND METHODS

DESIGN

The primary objectives were to evaluate the feasibility, safety, tolerability, and MTD of fractionated ^{90}Y-hPAM4 in combination with low-dose gemcitabine (200 mg/m^2) in a single cycle or in optional repeated cycles. Secondary objectives included assessment of tumor targeting, biodistribution, organ dosimetry, pharmacokinetics, immunogenicity, and efficacy (as determined according to Response Evaluation Criteria in Solid Tumors [RECIST], changes in CA19-9 serum titers, and survival).

PATIENTS

Previously untreated adults with histologically or cytologically confirmed stage III PDC (locally advanced, unresectable; N = 5) or stage IV PDC (metastatic; N = 33) had to have a Karnofsky performance status ≥70 and adequate hematologic parameters (eg, hemoglobin ≥11 g/dL, absolute neutrophil count ≥2.0 × 10^9/L, platelets ≥150 × 10^9/L). Additional eligibility requirements included life expectancy >3 months, no known history of active cardiac or pulmonary disease, no major surgery within 4 weeks, and adequate renal and hepatic function at study entry (creatinine and bilirubin levels ≤1.5 times the institutional upper limit of normal and aspartate and alanine aminotransferase levels ≤2.0 times the institutional upper limit of normal). Patients were excluded if they had disease that was metastatic to the central nervous system; a single tumor mass that measured >10 cm in greatest dimension; grade >2 anorexia, nausea, vomiting, or signs of intestinal obstruction; known human immunodeficiency virus or hepatitis B or C positivity; or other concurrent medical or psychiatric conditions that could confound study interpretation or prevent the completion of study procedures.

The institutional review board at each participating site approved the study, and written informed consent was obtained from all patients. This study is registered as National Clinical Trial NCT00603863.

Treatment—Each treatment cycle was 4 weeks (Fig. 1). A 10-mg kit of 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetra-acetic acid (DOTA)-conjugated hPAM4 was labeled at local radiopharmacies.[17,18] Patients received indium-111-labeled hPAM4 (^{111}In-hPAM4) (3–5 mCi, 111–185 MBq) the first week to assess pharmacokinetics, antibody biodistribution, and radiation dosimetry estimates for ^{90}Y-hPAM4, which was administered intravenously over 10 minutes without premedication once weekly for the next 3 weeks. Patients received gemcitabine (200 mg/m^2 intravenously over 30 minutes) once weekly for 4 weeks at least 2 days after the radioimmunoconjugate to permit adequate antibody accumulation at tumor sites before initiating radiosensitization based on prior studies.[12–14]

Dose-limiting toxicity (DLT) was defined for each treatment cycle as grade 4 hematologic toxicity that lasted ≥7 days or failure to recover to grade 1 within 12 weeks of completing a cycle, allowing supportive measures to aid recovery. Grade 4 nonhematologic toxicity of any duration and grade 3 toxicity that lasted ≥5 days also were considered DLTs. Transfusions and growth factors were permitted. At the discretion of the investigator, patients who completed a treatment cycle without DLT or overt progression of disease were eligible to receive additional treatment cycles at the same dose level after their hematologic toxicity recovered to grade 1 (typically 4–8 weeks later), which was at the discretion of the investigator.

A standard 3 + 3 dose escalation design was used to determine the MTD of the ^{90}Y dosing for the initial treatment cycle, exploring dose levels of 6.5 mCi/m^2 (241 MBq/m^2), 9.0 mCi/m^2 (333 MBq/m^2), 12.0 mCi/m^2 (481 MBq/m^2), and 15.0 mCi/m^2 (555 MBq/m^2) weekly for 3 weeks in the first part of the trial. In the second part, additional patients were enrolled to gain further experience at the ^{90}Y MTD of the first cycle (12 mCi/m^2 weekly for 3 weeks) and at the next lower level (9.0 mCi/m^2 weekly for 3 weeks).

Study Assessments—Pharmacokinetics, imaging and dosimetry procedures have been reported.[19–21] Evidence of tumor targeting was not required. To proceed with treatment, dose estimates for each cycle were required to be <300 centigrays (cGy) for red bone marrow, <3000 cGy for liver, and <2000 cGy for kidney and lung.[20,21] Anti-hPAM4 antibody response (HAHA) was assessed by using an enzyme-linked immunosorbent assay at baseline and at monthly intervals.[17]

Adverse events were classified according to the Medical Dictionary for Regulatory Affairs (MedDRA Maintenance and Support Services Organization, Northrop Grumman Information Systems, Chantilly, Va) and were graded according to version 3.0 of the National Cancer Institute's Common Terminology Criteria for Adverse Events. Serum chemistry levels, physical examinations, vital signs, and urine analyses were performed over 12 weeks after treatment, and weekly or more frequent blood counts were obtained for grade ≥2 cytopenias. Serum levels of CA19-9 were obtained at baseline and then at 4 weeks, 8 weeks, and 12 weeks after treatment. Computed tomography (CT) scans were evaluated by local radiologists at baseline and then until progression or at 4 weeks, 8 weeks, and 12 weeks after RAIT, and the best treatment response at any of these evaluations was classified according to RECIST as a complete response (CR), a partial response (PR), stable disease (SD), or progressive disease (PD).[22] ^{18}F-FDG-PET or PET/CT imaging was optional.

Statistical Analyses—Response rates were summarized using descriptive statistics. Overall survival (OS) was calculated from the first ^{90}Y-hPAM4 dose to death or last contact. The duration of response was determined from the onset to the earliest occurrence of progression, death, or last contact. The probability of survival was estimated using the Kaplan-Meier method.

RESULTS

Forty-two adult patients with untreated stage III or IV PDC were enrolled. All had CT-measurable disease, primarily involving the pancreas and/or liver, and most had elevated baseline CA19-9 serum levels (Table 1).

Treatment

Sixteen patients were treated during the first part of the trial and received their initial treatment cycle of ^{90}Y-hPAM4 weekly for 3 weeks at doses of 6.5 mCi/m^2 (N = 4), 9.0 mCi/m^2 (N = 4), 12.0 mCi/m^2 (N = 3), and 15.0 mCi/m^2 (N = 5). There were no DLTs except for 1 patient at the 15.0 mCi/m^2 dose level who had grade 4 platelets that lasted >7 days. However, further enrollment at the 15.0 mCi/m^2 dose level was not pursued, because 2 patients who initially were assigned to this level had required a dose reduction to meet the protocol-defined radiation dose restrictions to red bone marrow. Thus, after enrolling 3 more patients at the 12.0 mCi/m^2 dose level without DLT and without having to reduce the dose because of dosimetry concerns, the MTD for the initial treatment cycle effectively was declared as 12.0 mCi/m^2 weekly for 3 weeks. Nineteen additional patients were then treated during the second part of the study, including 11 patients at the MTD of 12.0 mCi/m^2 weekly for 3 weeks and 8 patients at the next lower level (9.0 mCi/m^2 weekly for 3 weeks),

the latter patients being added because of concern that treatment at the single-cycle MTD level would compromise repeated cycles at the same dose level.

In total, 38 patients were treated, including 14 who had overt PD on CT scans at their first post-treatment evaluation and were ineligible for additional cycles. Although retreatment of the other 24 patients was at the investigator's discretion, 11 patients were either removed from the study either to hospice or to pursue other treatment options. Thus, 25 patients received only 1 cycle, whereas 13 received 1 to 3 more treatment cycles, all at the same ^{90}Y dose level as their first cycle (Table 2).

Adverse Events

Treatment was well tolerated, and no infusion reactions were reported. Thus, as expected, the main toxicity was hematologic, and there were dose-limiting cytopenias, which are detailed below. No abnormal patterns of changes occurred in standard serum chemistries, and no grade 3/4 adverse events were reported except for several isolated elevations of transaminases, alkaline phosphatase, or bilirubin, consistent with hepatic involvement, biliary obstruction, and other abdominal disease complications (data not shown). Most of the adverse events reported reflected gastrointestinal or hepatobiliary complications, pain or constitutional complaints expected in this population with advanced PDC, or cytopenias expected from treatment with RAIT and gemcitabine. Fifteen patients had 17 serious adverse events, including biliary or gastrointestinal obstruction (N = 5); febrile neutropenia (N = 3); and anemia, pneumonia, pretreatment cerebrovascular events, splenic abscess, mental status change, pleural effusion, ascites, hyponatremia, and prolonged thrombocytopenia complicated by rectal bleeding attributed to gastrointestinal tumor invasion (N = 1 each). Thirteen patients had 19 infections, which were treated with either intravenous antibiotics (febrile neutropenia, N = 3; pneumonia, ascending cholangitis, splenic abscess, urinary tract infection, N = 1 each) or orally (thrush, N = 4; urinary tract infection, N = 3; superficial lesions, N = 2; shingles, upper respiratory infection, *Helicobacter pylori*, N = 1 each). No therapy-related major bleeding or other significant adverse events occurred.

Myelosuppression and Dose-Limiting Toxicity

For the 38 treated patients, grade 4 anemia occurred only at the highest dose level, and grade 3 anemia was infrequent. However, grade 3/4 neutropenia or thrombocytopenia developed in 20 of 38 patients (53%) after cycle 1 and developed in all retreated patients. For patients with grade 3/4 events, the median time from the first dose of ^{90}Y-hPAM4 to their nadir was 3.8 weeks for platelets and 4.2 weeks for neutrophils during the first cycle, with similar times to nadirs after subsequent cycles (data not shown). For cycle 1, the incidence of grade 3/4 neutropenia or thrombocytopenia among the 38 treated patients increased with dose levels, but there were only 3 DLTs (1 each at the 3 higher dose levels, all grade 4 thrombocytopenia that lasted 1–2 weeks), and all cytopenias recovered from grade 3/4 nadirs to grade 1 within a median of 1.9 weeks (maximum, 5.4 weeks) for platelets and 1.4 weeks (maximum, 4.1 weeks) for neutrophils. In the second cycle, 3 of 4 patients who were retreated at dose levels ≤9.0 mCi/m^2 weekly for 3 weeks had grade 3/4 cytopenias, but only 1 patient at the 9.0 mCi/m^2 weekly for 3 weeks dose level had a DLT (grade 4

thrombocytopenia for 10 days that was still grade 3 at 12 weeks). However, all 9 patients who were retreated at dose levels ≥12.0 mCi/m^2 weekly for 3 weeks had grade 3/4 cytopenias in the second cycle, often requiring transfusions, including 6 patients with DLTs (5 patients had thrombocytopenia that lasted >7 days, including 4 who still had grade 3/4 thrombocytopenia at 12 weeks). Finally, 2 patients at 6.5 mCi/m^2 weekly for 3 weeks encountered grade 3/4 cytopenias after receiving 3 or 4 cycles, including 1 DLT because of prolonged grade 4 thrombocytopenia. After completing this study, 20 patients received chemotherapy, predominantly gemcitabine alone or in combination with 1 or more other drugs (capecitabine, fluorouracil, oxaliplatin, docetaxel, and erlotinib), indicating that the myelosuppression from RAIT was reversible and did not affect patients' ability to receive other forms of therapy after participating in this study.

Pharmacokinetics, Biodistribution, and Tumor Targeting

The mean ± standard deviation decay-corrected serum half-life of ^{111}In-hPAM4 was 3.8 ± 0.7 days (range, 1.7–4.8 days) for all 38 patients in the first cycle and 3.7 ± 0.9 days (range, 2.4–5.4 days) for 13 retreated patients in the second cycle. ^{111}In-hPAM4 imaging at each cycle revealed a normal antibody biodistribution pattern and no obvious changes with retreatment except for 2 patients who had rapid antibody blood clearance to the liver, which made them ineligible for treatment.

Radiation Dosimetry Estimates

Normal organ radiation doses for the first and second cycles in the same patients were not substantially different and were similar to those reported in the previous study.[17] For example, a single cycle of treatment at the 12.0 mCi/m^2 weekly for 3 weeks dose level resulted in cumulative radiation doses of 878 cGy (range, 417–1577 cGy) to the kidneys, 1272 cGy (range, 758–1948 cGy) to the liver, 701 cGy (range, 524–997 cGy) to the lungs, and 233 cGy (range, 154–312 cGy) to the red bone marrow. Even with repeated cycles, the total cumulative dose still generally remained below the standard limits for the solid organs, but the combined cumulative dose to the red marrow was 510 cGy (range, 399–638 cGy). An example of antibody targeting is provided in Figure 2 along with radiation dose estimates calculated for the primary tumor (range, 39–44 grays).

Immunogenicity

Of the 32 treated patients who had adequate samples for HAHA assessment, only 1 patient developed an elevated titer of uncertain clinical significance (750 ng/mL 8 weeks after the initial treatment cycle, decreasing over time).

Treatment Responses

Of the 38 patients who received treatment, CT-based evaluations revealed PRs according to RECIST and stabilization for all dose levels (Table 3). One patient had SD after the first treatment cycle that converted to a PR after a second treatment cycle; otherwise, all of the best responses occurred after the first cycle. The overall disease control rate (CR + PR + SD, N = 22) was 58%, including 6 patients (16%) with PRs (all with stage IV disease) and 16 patients (42%) with stabilization as their best response. All 5 patients with stage III disease

had SD, whereas 52% of patients with stage IV disease had disease control (PR, 6 of 17 patients; SD, 11 of 17 patients). The median duration of disease control was 3.9 months (95% confidence interval [CI], 2.2–6.5 months) for all 22 patients, including 3.6 months (95% CI, 2.3–8.4 months) for the 6 patients with PRs.

Twenty-seven treated patients had elevated serum CA19-9 levels at baseline and had at least 1 CA19-9 result after the first cycle before initiating additional cycles. The overall response rate was 33%, based on decreases >50% from baseline levels after the first cycle at all dose levels. Twenty-six percent of patients had a response based on a more stringent decrease of >75%.

Twenty-five treated patients had positive baseline FDG-PET studies with at least 1 PET study available after the first cycle before receiving additional treatment cycles. Standard uptake values (SUVs) were obtained for all index lesions. Responses were based on decreases of >25% from baseline for all index lesions or >50% for just the baseline lesion with maximal SUV value. PET-SUV decreases occurred at all dose levels, with overall response rates of 52% (all index lesions) and 36% (maximal baseline lesion only). Examples of PET responses to treatment are provided in Figure 2.

Survival

Of the 38 treated patients, 5 remained alive 15 to 25 months after starting treatment. Kaplan-Meier estimated OS curves are provided in Figure 3. The 38 treated patients had a median OS of 7.7 months (95% CI, 5.6–9.6 months); and 58% (22 of 38 patients) survived for ≥6 months; 26% (10 of 38 patients) survived for ≥1 year, and 46% (6 of 13 patients) of patients in the repeated cycle group were alive at >1 year. The median OS was 6.0 months (95% CI, 5.2–8.0 months) for 33 patients with stage IV disease and 19.6 months (95% CI, 7.9–24.3 months) for 5 patients with stage III disease. The 16 patients who were treated at the 2 lowest dose levels (6.5 mCi/m^2 and 9.0 mCi/m^2 weekly for 3 weeks) had a median OS of 6.3 months (95% CI, 3.0–12.1 months), and 2 patients remained alive at 15 months. The 22 patients who were treated at the 2 highest dose levels (12.0 mCi/m^2 and 15.0 mCi/m^2 weekly for 3 weeks) had a median OS of 8.0 months (95% CI, 5.6–9.8 months), and 3 patients remained alive at 21 to 25 months. Assessing the impact of retreatment, 6 of those 13 patients (46%) survived for ≥1 year and had a median OS of 11.8 months (95% CI, 8.0–13.5 months) compared with 5.4 months (95% CI, 3.0–8.0 months) for the 25 patients who received only 1 treatment cycle ($P < .034$; log-rank test). Among the 13 patients who received ≥2 more cycles, 3 patients with stage III disease had a median OS of 24.3 months, whereas the remaining 10 patients had a median survival of 10.7 months.

DISCUSSION

Therapy with radiolabeled antibodies has achieved success in lymphomas, but objective responses rarely are reported in solid tumors with single-dose RAIT.[23] Only limited efforts involving dose fractionation or administration with other systemic and potentially radiation-enhancing drugs have been undertaken.[24–26] To our knowledge, this is the first study describing the combination of a drug and RAIT as active in a solid tumor and particularly in a challenging disease like advanced PDC. In the first study of pretreated patients with PDC

who received a single dose of ^{90}Y-hPAM4, several patients had transient responses by CT,[17] suggesting that the radiolabeled antibody was active by itself. This is encouraging, because objective responses rarely occur with standard doses of gemcitabine and erlotinib.[2] The hypotheses for this study were: 1) RAIT fractionation would be more potent with less myelosuppression, 2) combination with a low gemcitabine dose of 200 mg/m^2 weekly for 4 weeks would further potentiate therapeutic benefit without substantially increasing toxicity, and 3) repeated cycles would be more effective than a single cycle. These hypotheses were confirmed. The imaging, pharmacokinetic, and radiation dosimetry data obtained at the first cycle in this study were similar to those reported with single-dose RAIT without gemcitabine in the previous study,[17] and there were no changes in these parameters with repeated cycles. The ^{90}Y-hPAM4 administrations were well tolerated with no infusion reactions. After completing this investigational treatment, 20 of 38 patients were able to receive various regimens of chemotherapy at different times during the course of their later therapy despite the dose-related myelosuppression induced with RAIT. Thus, combined RAIT plus chemotherapy may not limit subsequent chemotherapy.

With a median OS for all patients of 7.7 months, this regimen of a single treatment cycle provides evidence of modest antitumor activity for this combination therapy, especially because 5 patients with stage III disease contributed a median OS of 19.6 months. For those who received at least 2 treatment cycles, a median survival of 11.8 months was achieved; and, at 1 year, 46% remained alive (or 26% of all 38 patients who were treated at any dose). When considering only the 10 patients with stage IV disease, an median OS of 10.7 months was achieved. Repeated cycles will be required in future studies, but only approximately 33% of patients in the current study received additional cycles at the option of the managing physician. Nevertheless, these initial results appear promising, even compared with recent reports from other trials, because FOLFIRINOX (fluorouracil, leucovorin, irinote-can, and oxaliplatin) required a median of 10 cycles to achieve a median survival of 11.1 months, and 48.4% of patients remained alive at 1 year[4]: whereas the combination of gemcitabine plus nanoparticle albumin-bound paclitaxel (nab-paclitaxel) required a median of 6 cycles to achieve a median survival of 10.3 months, and similarly, 48% of patients remained alive at 1 year.[5] However, both of these therapy regimens had more severe adverse events, including neutropenia and febrile neutropenia[4] and more fatigue and sensory neuropathy,[5] than the reversible myelosuppression noted as the only major side effect in the current study. In this trial, most patients who received repeated cycles had a total of 8 very low doses of gemcitabine and 6 fractionated doses of RAIT; thus, the therapy was shorter in duration and less intensive than the other combination chemotherapy regimens. We appreciate that it is premature to compare our 1-arm, initial therapy trial with the other cited studies and that, as in most survival trials of investigational agents, further therapies administered also may contribute to improved patient outcome. Furthermore, the small number of patients who received repeated therapy cycles in this study could constitute a selection bias of patients with less aggressive disease.

Of the 38 treated patients, the overall disease control rate (CR + PR + SD) according to CT-based RECIST criteria was 58%, including 6 patients (16%) with PRs (all with stage IV disease) and 16 patients (42%) with SD as their best response, and approximately 66% received only a single therapy cycle. Metabolic imaging (PET) and biomarkers (CA19-9)

confirmed efficacy; after the first cycle, 52% of patients (13 of 25) had negative or >25% reduced uptake in all lesions by FDG-PET SUV values, and 33% of patients (9 of 27) who had elevated CA19-9 levels at baseline had decreases >50% in serum levels. Comparing results after the first cycle between patients treated at the 2 highest dose levels (≥12.0 mCi/m^2 weekly for 3 weeks) and patients treated at the 2 lowest dose levels (≤9.0 mCi/m^2 weekly for 3 weeks), 18% versus 6%, respectively, had CT-confirmed PRs; 44% versus 18%, respectively, had CA19-9 decreases; and 63% versus 33%, respectively, had PET-confirmed improvements. Hence, these parameters responded in a dose-dependent, concordant manner and are consistent with the experience reported with nab-paclitaxel combined with gemcitabine.[5]

In the current study, patients received the same ^{90}Y dose for each of their first or repeat cycles. And, as expected, the major toxicity was grade 3/4 neutropenia or thrombocytopenia, which increased with both dose level and retreatment. Although these findings generally are consistent with increasing radiation-absorbed doses to the red bone marrow, the current dosimetry methodology for predicting myelosuppression remains too limited to be applied on an individual basis other than to avoid exceeding generally accepted limits, which often are required for nonmyeloablative therapy studies. Here, this meant that the highest planned dose level of 15 mCi/m^2 weekly for 3 weeks was not pursued further after several patients had their dose reduced to remain within these limits. Then, patients initially were entered into the second part of the study at the maximally tolerated ^{90}Y dose level of 12 mCi/m^2 weekly for 3 weeks. This dose continued to be acceptable for the first cycle, because all cytopenias with follow-up were readily reversible with infrequently required hematologic support. However, the 12 mCi/m^2 dose appeared to be too high for retreatment, because several patients developed prolonged and transfusion-dependent thrombocytopenia after a second cycle. Therefore, subsequent patients were enrolled at 9.0 mCi/m^2. Although 1 patient at 9.0 mCi/m^2 developed thrombocytopenia that continued at grade 3 for at least 12 weeks, all other occurrences of cytopenias with retreatment at dose levels ≤9 mCi/m^2 were reversible.

Thus, based on the results from this phase 1 study, the maximum ^{90}Y dose selected for further clinical development in this population is 12.0 mCi/m^2 weekly for 3 weeks during the first cycle. However, because patients received the same dose for a second cycle in this study, the question of whether 9.0 mCi/m^2 weekly for 3 weeks or a lower dose would be suitable for follow-up as a retreatment cycle after 12 mCi/m^2 remains to be determined. Also, fractionated RAIT was administered only in combination with 4 weekly administrations of 200 mg/m^2 gemcitabine. Thus, studies are ongoing to determine acceptable ^{90}Y dosing for retreatment and whether higher gemcitabine doses are advantageous with RAIT.

In conclusion, this study confirmed the hypotheses that patients can tolerate higher cumulative radiation with fractionated dosing than with single doses and that low-dose gemcitabine can be combined effectively with repeated cycles of RAIT. Encouraging therapeutic activity and survival results were observed with this combination and will need to be confirmed in subsequent studies, including controlled trials. Finally, in a patient population often characterized by dismal outcome and poor quality of life, this novel

therapeutic approach was well tolerated, and it is noteworthy that it did not preclude patients from receiving subsequent chemotherapy during the course of their disease.

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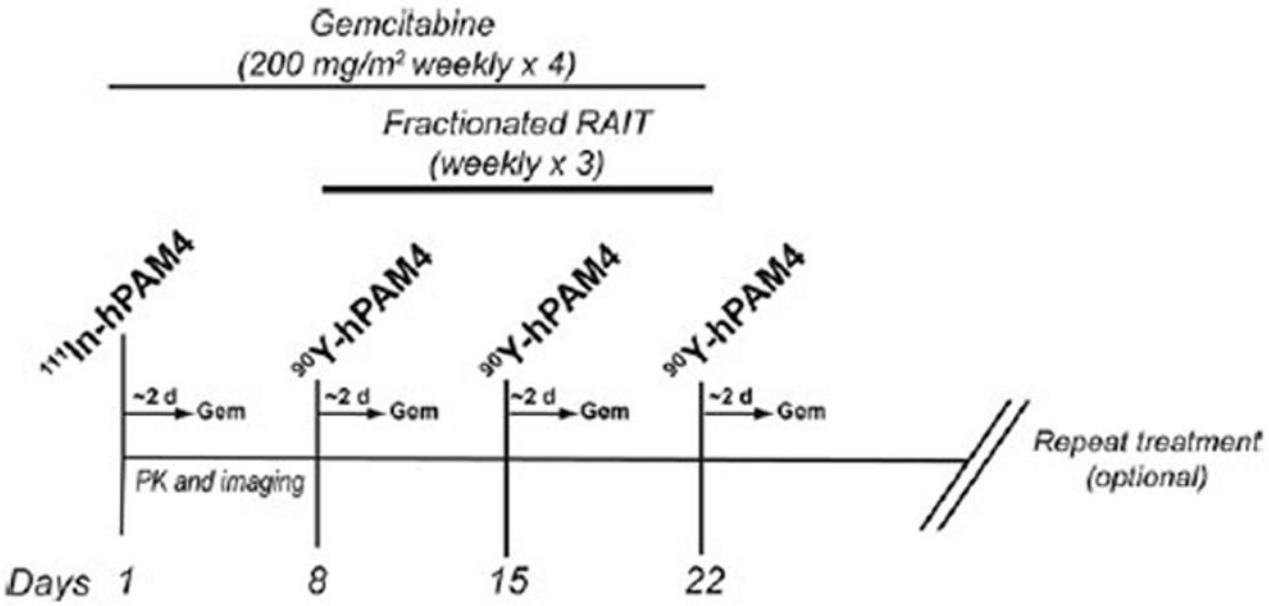

Figure 1.

This is the protocol schema. RAIT indicates fractionated radioimmunotherapy; ^{111}In-hPAM4, indium 111-labeled, humanized clivatuzumab tetraxetan; ^{90}Y-hPAM4, yttrium 90-labeled, humanized clivatuzumab tetraxetan; Gem, gemcitabine; PK, pharmacokinetics.

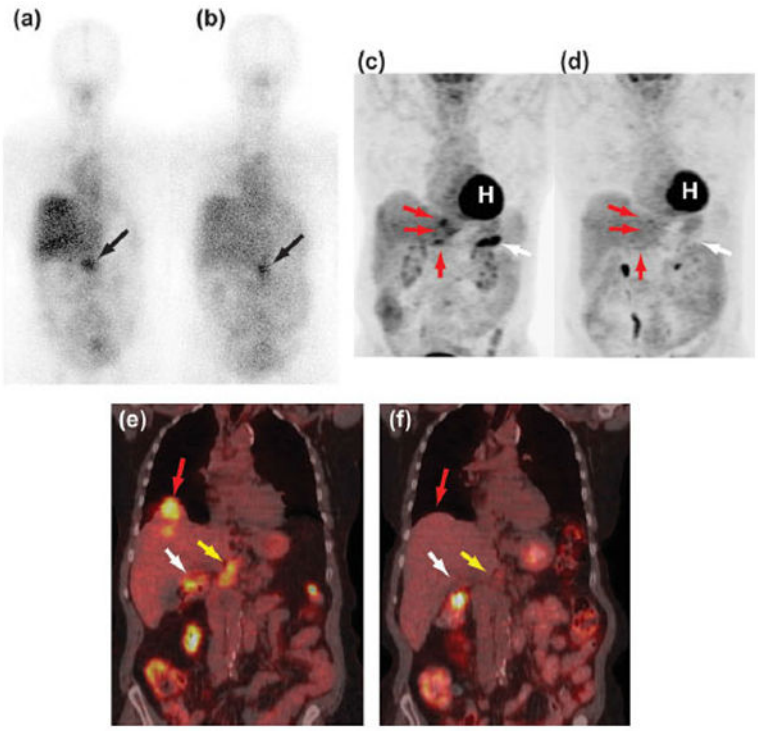

Figure 2.

These are examples of imaging from 3 patients. (a,b) These are anterior, planar indium 111-labeled, humanized clivatuzumab tetraxetan (^{111}In-hPAM4) images from 1 patient who received 2 treatment cycles, both at 12.0 mCi/m^2 weekly for 3 weeks. Uptake was observed at the site of the known primary pancreatic mass (arrows). (a) The pancreatic mass, initially measured as 3.7 × 2.6 cm, received 39 grays (Gy) in the first cycle. (b) After decreasing to 1.8 × 2.9 cm, the pancreatic mass received 44 Gy in the second cycle. The patient's disease remained stable until 8 weeks after the second treatment cycle, when disease progression occurred with the finding of new omental lesions. (c) Positron emission tomography–^{18}F-deoxyglucose (PET-FDG) imaging before treatment shows normal heart (H) activity and reveals uptake in the primary pancreatic tail mass (white arrow) and in 3 left-lobe liver metastases (red arrows). (d) The uptake is no longer apparent 4 weeks after treatment. Serum CA19-9 titers decreased from 1297 at study entry to 77 at 4 weeks after treatment. (e) In another patient, PET-FDG imaging before treatment reveals uptake in primary pancreatic mass (yellow arrow), in portacaval lymph nodes (white arrow), and in a large hepatic mass extending from the dome of the liver (red arrow). (f) The uptake is no longer observed 4 weeks after treatment.

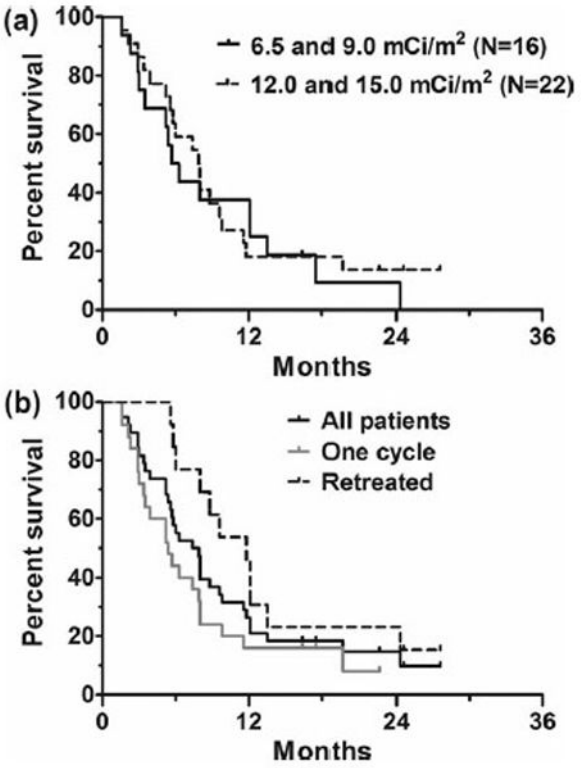

Figure 3.

These are Kaplan-Meier estimates of overall survival for all 38 treated patients. (a) Results at the 2 highest dose levels (12.0 mCi/m^2 and 15.0 mCi/m^2 weekly for 3 weeks) are compared with results at the 2 lowest dose levels (6.5 mC1/m^2 and 9.0 mCi/m^2 weekly for 3 weeks). (B) Results for all patients and for patients who were retreated are compared with results for patients who received only a single cycle of treatment.

Table 1

Demographics and Baseline Data (N = 42)

Variable	Value
Gender	
Men/women	26/16
Age	
Median (range), y	62.5 (40.3–86.6)
Race	
White	39
Black	1
Other	2
ECOG performance status	
0	19
1	22
2	1
Stage	
III (locally advanced)	6
IV (metastatic)	36
Time from diagnosis	
Median (range), mo	0.7 (0.1–3.3)
Prior therapy: No. of patients	
Chemotherapy[a]	0
External radiation	0
Surgery[b]	7
Stent placements[c]	6
CT-identified tumors[d]	
Lesion location: No. of patients	
Pancreas[e]	40
Liver[f]	23
Extrahepatic abdomen[g]	20
Chest/lung	3
Largest lesion: Median (range), cm	
Pancreas	4.6 (2.1–9.0)
Liver	2.4 (1.6–4.3)
Extrahepatic abdomen	1.8 (1.1–5.0)
Chest/lung	2.5 (1.1–3.4)
Hematology: Median (range)	
Hemoglobin, g/dL[h]	13.2 (9.9–15.7)
Neutrophils, K/μL	5.0 (2.7–12.7)
Platelets, K/μL	244 (123–595)
CA19-9: Median (range), U/mL	1534 (<1–257,560)

Variable	Value
No. with elevated CA19-9	35
No. with CA19-9 >1000 U/mL	23

Abbreviations: CT, computed tomography; ECOG, Eastern Cooperative Oncology Group.

[a]This was chemotherapy for advanced disease (1 patient had received gemcitabine, but as adjuvant therapy, 41 months earlier after undergoing pancreaticoduodenectomy).

[b]Surgery was palliative gastrojejunostomy with or without biliary bypass (N = 5) or pancreaticoduodenectomy but recurrence with advanced disease at study entry (N = 2).

[c]These included biliary stents (N = 5) and a gastrointestinal stent (N = 1).

[d]These were measurable tumor masses on baseline CT evaluation.

[e]A pancreatic mass was not present in 2 patients who underwent previous pancreaticoduodenectomy.

[f]These patients had 1 (N = 6), 2 (N = 7), 3 (N = 7), or more (N = 3) liver metastases.

[g]These patients had 1 (N = 10), 2 (N = 6), or more (N = 4) abdominopelvic lymph nodes, soft-tissue nodules, or implants.

[h]Two patients were granted waivers for hemoglobin levels <11 g/dL.

Table 2

Dose Levels and Treatment Cycles (38 Treated Patients)

				No. of Cycles[a, b]			
Dose Level	**GEM Dose: Weekly for 4 Weeks, mg/m^2**	**^{90}Y Dose: Weekly for 3 Weeks, mCi/m^2**	**No. of Patients**	**1**	**2**	**3**	**4**
1	200	6.5	4	2	0	1	1
2	200	9.0	12	10	2	0	0
3	200	12.0	17	10	7	0	0
4	200	15.0	5	3	2	0	0

Abbreviations: GEM, gemcitabine; ^{90}Y, yttrium 90.

[a]Of 38 treated patients, 25 patients received 1 cycle only; whereas 13 patients were retreated and received 2 cycles (N = 11), 3 cycles (N = 1), or 4 cycles (N = 1). The intention was for patients to receive retreatment at the same dose level as the first treatment cycle; however, 2 patients had minor dose reductions in their second cycle, including 1 patient who received 4.5 mCi/m^2 instead of 6.5 mCi/m^2 at the physician's discretion and 1 patient who received 13.1 mCi/m^2 instead of 15.0 mCi/m^2 to avoid exceeding normal organ radiation dose limits.

[b]The 5 treated patients with stage III disease included 1 patient who received 2 cycles at 9.0 mCi/m^2; 1 patient who received 1 cycle and 2 patients who received 2 cycles at 12.0 mCi/m^2; and 1 patient who received 1 cycle at 15.0 mCi/m^2.

Table 3

Post-Treatment Responses

	No. of Patients (%)	
CT: Best Response[a]	**Total No.**	**Disease Control: CR+PR+SD**	**PR+/SD**
Overall	38	22 (58)	6 (16)/16 (42)
Dose level			
1	4	3 (75)	1 (25)/2 (50)
2	12	5 (42)	1 (8)/4 (33)
3	17	12 (71)	3 (18)/9 (53)
4	5	2 (40)	1 (20)/1 (20)

		No. of Patients (%)	
CA19-9: Best Response to First Treatment Cycle[b]	**Total No.**	**>50% Decrease**	**>75% Decrease**
Overall	27	9 (33)	7 (26)
Dose level			
1	2	1 (50)	1 (50)
2	9	1 (11)	1 (11)
3	12	4 (33)	2 (17)
4	4	3 (75)	3 (75)

		No. of Patients (%)	
FDG-PET: Best Response to First Treatment Cycle[c]	**Total No.**	**All Index Lesions >25% Decrease[d]**	**>50% Maximum Lesion Decrease[e]**
Overall	25	13 (52)	9 (36)
Dose level			
1	2	2 (100)	2 (100)
2	7	1 (14)	0 (0)
3	11	7 (64)	4 (36)
4	5	3 (60)	3 (60)

Abbreviations: CR, complete response; CT, computed tomography; FDG-PET, positron emission tomography–18F-deoxyglucose; PR, partial response; SD, stable disease.

[a]The best response achieved is listed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0. No patient achieved a CR. All PRs occurred in patients with stage IV disease.

[b]These were 27 patients who had elevated baseline CA19-9 serum levels and achieved CA19-9 serum levels greater than or equal to baseline levels before receiving any retreatment.

[c]These were 25 patients who had positive baseline PET studies and had the same or improved post-treatment PET studies before receiving any retreatment.

[d]Each index lesion standardized uptake value decreased >25% from baseline.

[e]The lesion with highest pretreatment standardized uptake value (19 pancreatic primaries, 6 hepatic metastases) decreased >50% from baseline.