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Targeted radionuclide therapies for pancreatic cancer

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Abstract

Pancreatic malignancies, the 4th leading cause of cancer deaths, have an aggressive behavior with poor prognosis, resulting in a five-year survival rate of only 4%. It is typically a silent malignancy until patients develop metastatic disease. Targeted radionuclide therapies of cancer such as radiolabeled peptides which bind to the receptors overexpressed by cancer cells and radiolabeled antibodies to tumor-specific antigens provide a viable alternative to chemotherapy and external beam radiation of metastatic cancers. Multiple clinical trials of targeted radionuclide therapy of pancreatic cancer have been performed in the last decade and demonstrated safety and potential efficacy of radionuclide therapy for treatment of this formidable disease. While a lot progress has been made in treatment of pancreatic neuroendocrine tumors with radiolabeled with ^{90}Y and ^{177}Lu somatostatin peptide analogues, pancreatic adenocarcinomas remain a major challenge. Novel approaches such as peptides and antibodies radiolabeled with alpha emitters, pre-targeting, bispecific antibodies and biological therapy based on the radioactive tumorlytic bacteria might offer a potential breakthrough in treatment of pancreatic adenocarcinomas.

INTRODUCTION

Pancreatic malignancies, the 4th leading cause of cancer deaths, have an aggressive behavior with poor prognosis, resulting in a five-year survival rate of only 4%. It is typically a silent malignancy until patients develop metastatic disease (1). Pancreatic cancers can be divided in two main groups: cancers that occur in the exocrine or “non-endocrine” parts of the pancreas account for most of pancreatic malignancies, dominated mainly by pancreatic invasive or ductal adenocarcinomas; and endocrine pancreatic malignancies which can be divided into “functioning” (insulinomas, gastrinomas, glucagonomas, somatostatinomas) and “non-functioning” types. Unfortunately, available therapy options such as gemcitabine

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

and erlotinib have no significant impact on patients survival (2–4) and development of new effective treatments is needed to enhance and/or complement current available treatments. Targeted radionuclide therapies of cancer such as radiolabeled peptides which bind to the receptors overexpressed by cancer cells and radiolabeled antibodies to tumor-specific antigens provide a viable alternative to chemo- and external beam radiation therapies of metastatic cancers, including pancreatic cancer (5). Here we review the recent developments in targeted radionuclide therapies of pancreatic cancer.

RADIOLABELED PEPTIDES

Clinical studies

Although rare, pancreatic neuroendocrine tumors remain one of the most common abdominal neuroendocrine tumors, frequently presenting in advanced stages with associated challenging treatment (6). Somatostatin analogs such as Octreotide bind to somatostatin receptors usually expressed on well-differentiated neuroendocrine neoplasms and have been used for therapy of neuroendocrine pancreatic cancers. DOTATATE, an amide of the acid DOTA and (Tyr^3)-octreotate, has been labeled with different radionuclides for diagnosis (mainly ^{111}In and ^{68}Ga) and treatment (mainly ^{177}Lu and ^{90}Y) of neuroendocrine cancers.

Sansovini and his group studied activity and safety of ^{177}Lu-DOTATATE peptide receptor radionuclide therapy in patients with advanced G1/G2 pancreatic neuroendocrine tumors (Table 1). 26 patients received a mean complete dose of 25.5 GBq ^{177}Lu-DOTATATE while 26 patients received the renal and hematologic corrected mean dose of 17.8 GBq. They observed antitumor activity at both full and renal/hematological corrected dosages, but a significantly longer progression-free survival was achieved after a cumulative dose of 27.8 GBq(7). Ezziddin and colleagues presented a case report showing the potential of preoperative peptide receptor radionuclide therapy (PRRT) to downstage inoperable pancreatic neuroendocrine carcinoma patients for possible surgical resection. This patient had metastatic disease to the liver, mesenteric root infiltration and congestion of the superior mesenteric vein. After 3 cycles of ^{177}Lu-DOTA-octreotate (total of 21.2 GBq at 3-month intervals) patient achieved partial response with significant receptor downsizing and downstaging to Whipple surgery. Histopathology and subsequent imaging confirmed complete resection, with complete local remission on 22 months follow-up (8). Kaemmerer and colleagues presented an 33 year-old female patient with inoperable stage IV highly differentiated neuroendocrine pancreatic carcinoma who failed somatostatin analogue therapy and refused chemotherapy. She received two cycles of ^{90}Y-DOTATATE (62.1 and 121.6 mCi) as first line therapy combined with aminoacid infusion to avoid renal toxicity. There was a significant tumor response enabling successful complete surgical resection with subsequent complete remission for 18-month follow-up. The only observed adverse effects were mild anemia and erythrocytopenia (6). Delpassand et al presented a Phase 2 nonrandomized clinical trial, which included 37 patients with grades 1 and 2 disseminated and progressive gastroenteropancreatic neuroendocrine tumor (NET) who received 200 mCi ^{177}Lu-DOTATATE cycles, up to a cumulative dose of 800 mCi (Table 1). Thirty two patients were evaluated showing 28% partial response, 3% minimal response, 41% stable disease and 28% progressive disease. Therapy response was inversely associated with

hepatic disease involvement and there was no evidence of renal or hematologic toxicity. After ^{177}Lu-DOTATATE therapy, there was a significant upgrade in quality of life and performance status (9).

Insulinoma is a rare pancreatic neuroendocrine tumor and only 10% are considered malignant. Different treatment strategies have been used to balance insulin hypersecretion and subsequent hypoglycemia in those patients, but its control remains a challenge(10). van Schaik et al studied five patients with inoperable metastatic pancreatic insulinomas (metastases to liver, lymph nodes and/or bones) resulting in poorly controlled hypoglycemia requiring continuous glucose infusion who were either unresponsive or intolerant to conventional medications. Enrolled patients had no prior therapy with a different radiolabeled somatostatin analog and showed ^{111}In-DTPA-octreotide uptake higher than normal liver uptake on pre-therapy scan. One patient was treated with 10–11 GBq of ^{111}In-DTPA-octreotide at 4-week intervals and four patients received 3.7 GBq to 7.4 GBq of ^{177}Lu-octreotate at 6 to 10-week intervals. Radiolabeled somatostatin analogs controlled tumor growth and severe hypoglycemia in patients with malignant insulinomas with subsequent survival improvement. (10)

Fischbach and colleagues presented a case report of a 43 year-old woman admitted for recurrent syncope episodes secondary to hypoglycemia who was found to have multiple hepatic lesions on MRI. ^{18}FDG PET-CT scan showed a primary tumor in the pancreatic tail, subsequently confirmed well-differentiated pancreatic neuroendocrine tumor, as well as regional lymph nodes and hepatic metastases. Patient received a combination of ^{90}Y-DOTATATE and octreotide with resulting stable glycemia and partial response of liver metastases(11). Sainz-Esteban et al presented a patient with metastatic pancreatic vasoactive intestinal peptide secreting tumor who previously did not respond to high doses of octreotide analog. This patient received 2 cycles of 5 GBq ^{90}Y-DOTATATE at 3-month interval with subsequent reduction of vasoactive intestinal polypeptide levels as well as significant decrease of somatostatin receptor expression and tumor volume on ^{68}Ga-DOTANOC PET/CT images. Patient developed mild hematotoxicity (grade 1 erythrocytopenia), there was no evidence of nephrotoxicity and symptoms completely resolved on 4 years follow- up (12).

Sowa-Staszczak et al analyzed peptide receptor radionuclide therapy efficacy in non-functioning pancreatic neuroendocrine tumors (Table 1). Thirteen patients received 4–5 infusions of 11.1 – 15.54 GBq of ^{90}Y-DOTATATE while one patient received a combination of ^{90}Y/^{177}Lu-DOTA-TATE (total activity 10.36 GBq). To avoid renal toxicity, an amino acid formula was also administered before and after each radionuclide therapy. They concluded that PRRT is safe and effective in non-functioning pancreatic neuroendocrine tumors resulting in either disease regression or stabilization in most patients. There was no statistically significant survival difference in non-functional pancreatic neuroendocrine tumors when compared to other NETs post PRRT (13).

Safety aspects of radio labeled peptide therapy of pancreatic cancer are really important as bone marrow suppression, especially lymphocytic toxicity, is a known dose-limiting adverse effect for PRRT as lymphocytes express somatostatin receptors. Sabet et al analyzed long-

term severity, incidence, and reversibility of hematotoxicity on patients with metastatic neuroendocrine tumors who were treated with peptide receptor radionuclide therapy (PRRT) ^{177}Lu-octreotate. Two hundred and three patients with metastatic neuroendocrine tumors received 632 courses of ^{177}Lu-octreotate (mean dose of 7.9 GBq) with a goal of 4 therapies at 3-month interval. 1.4% developed delayed myodysplastic syndrome and 23 patients had grade 3 or 4 reversible hematotoxicity (2.7% leukopenia and 1.7% thrombocytopenia) with a mean recovery time of 12 months after completion of therapy (range 3–22 months), infrequently demanding clinical intervention. The only significant risk factors contributing for myelosuppression were prior cytopenia and cumulative administered dose, while splenectomy showed inverse association with leukopenia and thrombocytopenia. (14) Sierra et al followed16 patients with neuroendocrine cancers who were treated with ^{90}Y-DOTATOC, ^{177}Lu-DOTATATE, or both. Grade 2 to 3 lymphoid toxicity was noted, mostly involving B-cell line, and predominantly after therapy with ^{90}Y-DOTATOC. However, adverse effects were temporary with complete improvement at 3-month follow up. The lack of clinically significant adverse effects in those patients was explained by relative sparing of T-cells, opening possibilities for new therapies for B-cell lymphoproliferative diseases (15). Overall, PRRT of NET has produced encouraging results with manageable toxicities and has already become the standard of care in some European countries such as Germany.

Experimental studies

de Jong et al studied Lewis mice containing small (0.5 cm^2) and large (7–9 cm^2) volumes of CA20948 mouse pancreatic cancer in their flanks which express somatostatin receptors. They studied the therapeutic results of 60 Gy tumor radiation dose using ^{90}Y-DOTA-Tyr3-octreotate, ^{177}Lu-DOTA-Tyr3-octreotate and their combination. All 3 groups achieved therapeutic results in this mouse tumor model but the 50/50% ^{90}Y- and ^{177}Lu-labeled analogs combination produced higher antitumor results in animals with cancers of different sizes than either of them separately (16). Norenberg and his group studied the radiolabeling process of somatostatin analogue DOTATOC labeled with alpha emitter high-linear energy transfer (LET) ^{213}Bi tracer in a preclinical animal model as well as its stability, receptor specificity (biodistribution), safety, toxicity and therapeutic results when administered to the tumor bearing Lewis rats. Their results demonstrated >95% radiochemical purity with >=99.9% incorporation yield for ^{213}Bi-DOTATOC and specifically binding to tissues expressing somatostatin receptors. Lewis rats which received doses of 20 MBq or higher demonstrated more significant tumor shrinkage than rats which received 11 MBq or less, clearly demonstrating the dose response in tumor volume decrease - with minimal resulting toxicity(17).

RADIOLABELED ANTIBODIES

Clinical studies

Antibodies recognize their respective antigens with tremendous specificity. This characteristic over the years has fueled evolvement of research projects based on the use of monoclonal antibodies as delivery vehicles for radionuclides to achieve better imaging and therapy of cancer (18). In the ideal case, a cancer patient would first receive a diagnostic

dose of an antibody labeled with a radionuclide compatible with imaging procedures and a subsequent therapeutic dose of the same labeled antibody with curative intention, if sufficient antibody localization at the site of disease is achieved during the initial diagnostic stage. Factors like murine origin of monoclonal antibodies, and insufficient radiation dose delivered to neoplastic masses to induce objective responses and cures, have substantially affected efforts in this direction. Nonetheless, to improve overall survival and prognosis of neoplastic conditions like pancreatic cancer and to decrease mortality, radiolabeled antibodies present a novel therapeutic approach. Radiolabeled antibodies can target cancer specific antigens on pancreatic cancer cells, with potential tumoricidal activity. Numerous studies in literature have examined the possible therapeutic role of radiolabeled antibodies in management of pancreatic cancer.

Sultana and colleagues assessed the efficacy and safety of KAb201 which is an anti-carcinoembryonic antigen monoclonal antibody labeled with ^{131}I, in pancreatic cancer patients (Table 1). Twenty five patients with biopsy proven inoperable adenocarcinoma of the head of pancreas were included in the study and were randomized to receive KAb 201 via either intra-arterial or intravenous delivery route. 33% of patients demonstrated dose limiting toxicity in the intraarterial arm at 50 mCi, while 16% showed the same toxicity in the intravenous arm. The overall response rate was found to be 6%, and there was no appreciable difference in median overall survival (which was 5.2 months) between the intravenous and intraarterial arms. The authors concluded that dose limiting toxicity for ^{131}I-labeled KAb201 by the intraarterial route was 50 mCi, while it was not reached in the intravenous arm (19).

Gulec et al in a Phase I study attempted to assess the role of a single dose of ^{90}Y-clivatuzumab tetraxetan (^{90}Y-labeled hPAM4) which binds a mucin glycoprotein expressed in pancreatic adenocarcinomas (Table 1). Normal biodistribution was noted with ^{111}In-hPAM4 with radiation dose estimates to red marrow and solid organs acceptable for radioimmunotherapy. Tumor targeting was achieved in 12 out of 21 total patients. It was concluded that ^{90}Y-Clivatuzumab tetraxetan was well tolerated with manageable hematologic toxicity at the maximal tolerated ^{90}Y dose, and thus would constitute a potential new treatment agent for patients with advanced pancreatic cancer. The study demonstrated mild adverse reaction to treatment with ^{90}Y-hPAM4, with potential treatment efficacy in patients with metastatic pancreatic cancer (post-treatment stabilization of tumor growth and decrease in Ca19-9 levels) (20). However, tolerance of multiple administrations of ^{90}Y-hPAM4 treatment was not investigated.

There is a well justified trend to combine radiolabeled antibodies with the approved drugs for treatment of pancreatic cancer such as gemcitabine. The reasons behind this trend are: a wide use of gemcitabine in pancreatic cancer patients (2–4), its radiosensitizing properties (21), and the fact that, clinically, low doses of gemcitabine with external radiotherapy are generally well tolerated (22). In this regard, Ocean et al investigated fractionated radioimmunotherapy combined with low-dose gemcitabine after establishing the maximum tolerated dose of single-dose 90Y-hPAM4 that produced objective responses in patients with advanced pancreatic ductal carcinoma (23). Their results demonstrated that combination therapy with fractionated radioimmunotherapy with 90Y-hPAM4 and low-dose gemcitabine

showed encouraging therapeutic efficacy and controllable myelosuppression in patients with advanced pancreatic ductal carcinoma. Overall, the most encouraging results of the clinical work on RIT of pancreatic adenocarcinoma so far have been obtained with the combination of RIT and gemcitabine. Further adjustment of the doses and timing of administration might lead to the increase in the numbers of patients achieving complete or partial response.

Experimental studies

^{131}I-labeled Nd2 monoclonal antibody was evaluated by Inui and colleagues to assess its biodistribution, radiolocalization, and radioimmunotherapeutic potential in athymic nude mice bearing human pancreatic carcinoma xenografts (24). The study demonstrated adequate tumor to background ratio for ^{131}INd2 antibody and its potential for the RIT of pancreatic cancer without major treatment side effects. Additionally, the augmented efficacy of combined misonidazole, a hypoxic cell radiosensitizer with ^{131}I Nd2 was also noted.

It is suggested that recombinant mouse/human chimeric monoclonal antibody A10 (ch-A10) and its Fab fragment (ch-Fab) react with carcinoembryonic antigen on different carcinomas of gastrointestinal origin (25). Kamigaki et al investigated the role of ^{125}I-labeled ch-A10 and ch-Fab in an antigen-positive human pancreatic carcinoma (BxPC-3) xenograft model (25). Their results suggested that radioiodine-labeled chimeric A10 antibodies show significant inhibition of tumor growth compared to control and thus could potentially be useful candidates for radioimmunotherapy and radioimmunodetection of pancreatic carcinomas. However, the only graft used in the study was medullary pancreatic carcinoma graft; chirrous type carcinoma which is the most common type in humans was not investigated in the study.

Research has shown that monoclonal antibody 17-1A can be of potential value in management of pancreatic cancer. The antigen recognized by MAb 17-1A is expressed by normal and malignant epithelial tissues including adenocarcinomas of the pancreas and stomach. The ability of MAb 17-1A to detect and possibly treat pancreatic carcinomas was studied by Maeda et al (26). MAb 17-1A was labeled with ^{125}I and ^{111}In and injected into nude mice bearing HuP-T4 xenografts, and the biodistribution of ^{111}In- and ^{125}I-labeled MoAb 17-1A was examined. The authors concluded that MoAb 17-1A binds selectively to human pancreatic carcinoma HuP-T4 with tumor uptake greater than surrounding normal tissues, suggesting that MoAb 17-1A may be useful in the radioimmunodetection and RIT of pancreatic adenocarcinomas. The use of targeted therapy with α-particles emitters in oncology is burgeoning worldwide. This is driven by the advantages of α-emitters over β-emitters, including very specific targeting of the diseased cells due to the α-particles' short 50–80 μm tissue range, and increased killing efficiency due to high linear energy transfer. This results in a controlled therapeutic modality with minimal normal tissue effects (27). Kurtzman and colleagues investigated the role of alpha emitters in treatment of pancreatic cancer compared with traditional beta emitters (28). They attached ^{212}Bi which is an alpha-emitting radionuclide to a monoclonal antibody that recognizes a cell surface antigen on human pancreatic cancer cells. It was found that the ^{212}Bi-antibody complex was approximately 20 times more efficient in tumoricidal activity than X-ray irradiation and 5 times more cytotoxic than an isotype-matched control antibody. It was concluded that alpha

emitters attached to monoclonal antibodies may be useful in vivo and in vitro for differentially killing target cell populations, especially those resistant to conventional therapy. Bryan and colleagues utilized a chimeric mAb chTNT3 which binds to single-strand DNA (ssDNA) and RNA released from non-viable cells in fast growing tumors (29). This approach is different from the described above as it targets not viable but dying tumor cells and relies on “cross-fire” effect from a radionuclide to kill viable tumor cells. chTNT3 mAb was radiolabeled with ^{213}Bi and nude mice carrying MiaPaCa-2 xenografts were given either ^{213}Bi-chTNT3 (700 μCi), gemcitabine, cisplatin, unlabeled chTNT3 or left untreated. RIT abrogated the tumors growth while tumors in control groups grew aggressively. Chemotherapy was less effective than RIT and toxic to mice while RIT did not have any side effects. The authors concluded that RIT with ^{213}Bi-chTNT3 was safe and effective in treatment of experimental pancreatic cancer in comparison with chemotherapy.

Mouse monoclonal antibody Nd2 (m-Nd2, mouse IgG1) labeled with ^{131}I has demonstrated effectiveness in in-vivo radioimmunotherapy to treat pancreatic cancer in various research models. Nishihara and colleagues examined if a mouse/human chimeric antibody Nd2 (c-Nd2) could trigger an antibody-dependent cell-mediated cytotoxicity in a mousemodel (30). Their results suggested that cytotoxicity of c-Nd2 towards pancreatic cancer cells during mixed with human leukocytes was induced by antibody-dependent cell-mediated cytotoxicity. The authors concluded that c-Nd2 can induce ADCC, and may have an immunotherapeutic potential in patients with pancreatic cancer.

As described previously, radiolabeled mAb-PAM4 has a diagnostic and therapeutic potential in patients with pancreatic carcinoma as demonstrated by various research trials. Gold et al investigated the ability of a novel PAM4-based, bispecific monoclonal antibody construct, TF10, to pre-target a radiolabeled peptide for improved imaging and therapy (31). This humanized, recombinant tri-Fab bispecific monoclonal antibody (bsmAb) was prepared using specificity for targeting pancreatic cancer of PAM4 and another Fab binding to a hapten (histamine-succinyl-glycine [HSG]). Nude mice with CaPan1 pancreatic cancer xenografts were used to examine the role of radiolabeled TF10 and/or TF10-pre-targeted hapten-peptide (IMP-288) in imaging and possible therapy of pancreatic cancer. Sixteen hours post-injection of ^{125}I-TF10 with blood levels decreasing to <1%, ^{111}In-IMP-288 was administered as part of the pre-targeting approach. Three hours later, intense uptake was seen within the tumors, while no targeting was observed in animals given only the ^{111}In-peptide. It was suggested that TF10/^{90}Y-peptide pre-targeting would be more tumoricidal than ^{90}Y-PAM4-IgG based on radiation dose estimates. TF10 pre-targeting may thus be of potential use in diagnosis and treatment of pancreatic cancer as compared with directly radiolabeled PAM4-IgG. Karacay et al in another study demonstrated that PAM4-based pre-targeted RIT with ^{90}Y hapten peptide is efficacious in pancreatic cancer therapy, with less toxicity than ^{90}Y-PAM4 IgG (32). Additionally, the authors emphasized that augmented response rates can be achieved if therapy is combined with gemcitabine and with dose fractionation of pre-targeted RIT.

As in the clinical studies, there is an interest among the research groups to combine different agents which would, hopefully, work synergistically and make pancreatic cancer treatment more effective. Al-Ejeh et al proposed an effective pancreatic ductal adenocarcinoma

(PDAC) treatment using a combination of chemotherapy (gemcitabine), Checkpoint kinase 1 (CHK1) inhibitor PF-477736, and epidermal growth factor receptor (EGFR)-targeted radioimmunotherapy (^{177}Lu-labeled anti-EGFR antibody) in cellline models and patient-derived xenografts. This combined triple therapy was well tolerated in mice and effective in PDAC tumors, representing a potential therapy option (33).

Chemoimmunotherapy with antibody-drug conjugates (ADC) is a potentially promising therapy for management of solid tumors. Sharkey and colleagues evaluated if ADC could be combined with radioimmunotherapy (RIT) to improve efficacy without increasing host toxicity (34). Antibody-SN-38 conjugates with marked antitumor activity in xenograft models at nontoxic doses were used in the study. Nude mice with human pancreatic cancer xenografts (Capan-1 and BxPC-3) were treated either with a single dose of ^{90}Y-labeled hPAM4 antibody or in combination with an anti-Trop-2-SN-38 conjugate. It was found that the combination therapy halted tumor progression and eliminated established xenografts markedly better than the individual treatments without appreciable toxicity. These studies demonstrated possible efficacy and safety of combined therapy with antibody drug conjugates (anti-SN 38 conjugate) and RIT (^{90}Y-hPAM4) for treatment of pancreatic carcinoma.

NEW APPROACHES

There is a growing interest in biological therapy of cancer based on tumorlytic viruses and bacteria. *Listeria monocytogenes* recently showed some promise as a part of cancer vaccine in patients with metastatic pancreatic cancer (35). Quispe-Tintaya et al. hypothesized that Listeria could be used to deliver therapeutic radionuclides emitting cytocidal beta-particles in a specific manner to the microenvironment of metastases and primary tumors and into tumor cells. To achieve this, they coupled 188Rhenium (^{188}Re), a high energy beta-emitting radionuclide with a short physical half-life of 16.9 hrs, to attenuated Listeria^{at} by utilizing a Listeria-specific antibody (36). Thus the first truly radioactive microbe for treatment of cancer, radiolisteria (RL) was created. The researchers then demonstrated using a highly metastatic pancreatic mouse tumor model (Panc-02) that RL was capable of delivering radioactivity to the metastases and less abundantly to primary tumors in vivo, without harming normal cells. Such specific delivery without the toxic side effects was possible because RL was efficiently cleared by the immune system in normal tissues but not in the heavily immune-suppressed microenvironment of metastases and primary tumor. Eleven treatments with low doses (10^4 colony forming units) of the RL resulted in a dramatic decrease in the number of metastases (>90%) compared with control groups in the Panc-02 model. In the Commentary on this work, Stritzker and Szalay stated that “taking these data together, the study by Quispe-Tintaya et al. clearly demonstrates the therapeutic benefit of a strategy combining the tumor targeting and biotherapeutic effects of *L. monocytogenes* with the cytotoxic effects of ^{188}Re-labeled antibodies administered as a single agent” (37).

CONCLUSIONS

Multiple clinical trials of radionuclide therapy of pancreatic cancer have been performed in the last decade and demonstrated safety and potential efficacy of radionuclide therapy for

treatment of this formidable disease. A lot progress has been made in treatment of pancreatic neuroendocrine tumors with radiolabeled somatostatin analogues which entered the realm of standard clinical care in some European countries. Hopefully, during the next decade PRRT will gain acceptance and FDA approval in the United States as well. Pancreatic adenocarcinomas, however, remain a major challenge. Further improvements in the combined treatment with RIT and gemcitabine. might lead to the increase in the numbers of patients achieving complete or partial response. We believe that in the coming years the novel approaches on using targeted alpha-emitters, biological agents or their combination will be translated into the clinic and will hopefully help to completely eradicate the metastatic pancreatic cancer.

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Table 1

Examples of clinical studies of radionuclide therapy of pancreatic cancer

Radionuclide therapy agent	Receptor/Antigen	Dose	Response rate	Toxicity	Reference
^{177}Lu-DOTATATE peptide	SSR	25.5 GBq (26 patients) 17.8 GBq (26 patients)	12% CR 27% PR 46% SD	No major acute or delayed hematological toxicity	7
^{177}Lu-DOTATATE peptide	SSR	7.4–29.6 GBq (37 patients)	28% PR 3% MR 41% SD 28% PD	No renal or hematological toxicity	9
^{90}Y-DOTATATE peptide	SSR	11.1–15.5 GBq (14 patients)	21.4% PR 42.9% SD 37.5% PD	No clinically significant hematological or renal toxicity	13
^{131}I-KAb201 antibody	CEA	Up to 1.85 GBq, intraarterial and intravenous delivery arms (25 patients)	Overall response rate 6%; median overall survival 5.2 months	1.85 GBq was dose-limiting toxicity in intraarterial arm; was not reached in intravenous arm	19
^{90}Y-clivatuzumab tetraxetan antibody	mucin	0.56–0.93 GBq (20 patients)	35% SD 15% PR 50% PD	Grade 3 to 4 neutropenia and thrombocytopenia increasing with ^{90}Y dose, most cytopenias recovered to grade 1 within 12 weeks	20

SSR-somatostatin receptors; CR-complete response; MR-minimal response; PR-partial response; SD-stable disease; PD-progressive disease

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