Immunotherapy updates in pancreatic cancer: are we there yet?

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Abstract: Pancreatic cancer is a lethal disease and remains one of the most resistant cancers to traditional therapies. Historically, chemotherapy or radiotherapy did not provide meaningful survival benefit in advanced pancreatic cancer. Gemcitabine and recently FOLFIRINOX (5-fluorouracil, leucovorin, oxaliplatin and irinotecan) have provided some limited survival advantage in advanced pancreatic cancer. Targeted agents in combination with gemcitabine had not shown significant improvement in the survival. Current therapies for pancreatic cancer have their limitations; thus, we are in dire need of newer treatment options. Immunotherapy in pancreatic cancer works by recruiting and activating T cells that recognize tumor-specific antigens which is a different mechanism compared with chemotherapy and radiotherapy. Preclinical models have shown that immunotherapy and targeted therapies like vascular endothelial growth factor and epidermal growth factor inhibitors work synergistically. Hence, new immunotherapy and targeted therapies represent a viable option for pancreatic cancer. In this article, we review the vaccine therapy for pancreatic cancer.

Keywords: immunotherapy, pancreatic cancer, vaccine

Introduction

Pancreatic cancer is the fourth leading cause of cancer-related death in men and women in the USA [Jemal *et al.* 2010]. There were 36,800 deaths from pancreatic cancer in the United States in 2010. In developing countries, there were an estimated 165,100 new cases and 161,800 deaths in 2011 [Jemal *et al.* 2011]. The 5-year survival is less than 5% for patients with metastatic pancreatic adenocarcinoma [Jemal *et al.* 2011]. Most pancreatic cancers are either locally advanced or metastatic at diagnosis. The survival for metastatic pancreatic cancer remains poor and less than 20% survive at the end of 1 year. Surgical resection and chemotherapy improve survival in early stage pancreatic cancer; the historical 5-year survival post resection remains approximately 15–20%, with 1- and 2-year survival of 60–67% and 35–45% respectively depending on the staging [Bilimoria *et al.* 2007]. There are only a few chemotherapy agents that have shown effect in pancreatic cancer to date, including gemcitabine and recently a combination of 5-fluorouracil (5-FU), leucovorin, oxaliplatin and irinotecan (FOLFIRINOX) [Conroy *et al.* 2011; Oettle *et al.* 2007]. Chemoradiation

has shown some benefit in locally advanced unresectable pancreatic cancers. The survival with these modalities is marginal and we are in urgent need of other therapies. Pancreatic cancer cells are resistant to chemotherapy or radiotherapy. Immune therapies act differently than chemotherapy or radiotherapy and might be an alternative treatment modality to this deadly disease with significantly less toxicity [Laheru and Jaffee, 2005]. Here we review the recent advances in immunotherapy for pancreatic cancer treatment.

Vaccines

Cancer vaccines are biological preparations that involve administering an antigen that is specific for a particular tumor type and boosts the body's natural ability to protect itself. There are a number of ways to deliver the vaccines. For example; whole-cell recombinant vaccines, dendritic cell (DC) vaccines that combine antigen with DCs to present to white cells, DNA vaccine by inserting viral or bacterial DNA into human or animal cells, or T-cell receptor peptide vaccines by inserting peptides to modulate cell-mediated immunity. Below, we discuss these categories in further detail.

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Whole-cell vaccines

Algenpantucel-L

Algenpantucel-L is the most clinically advanced and promising immunotherapy for pancreatic cancer. Algenpantucel-L is an irradiated, live combination of two human allogeneic pancreatic cancer cell lines that express the murine enzyme α -1,3-galactosyl transferase (α GT), which directs the synthesis of α -galactosyl (α Gal) epitopes on surface proteins and glycolipids of such cell lines. α Gal epitopes are absent in humans, but are present in nonprimate mammals, prosimians and New World monkeys [Galili *et al.* 1987]. Humans and apes have a nonfunctional gene for α GT and do not express α Gal epitopes. However, humans and apes have large quantities of the natural anti- α Gal antibodies [Galili *et al.* 1988]. The *in vivo* binding of anti- α Gal antibodies to α Gal epitopes in alenpantucel-L activates complement-mediated lysis and antibody-dependent cell-mediated toxicity toward algenpantucel-L cells, causing hyperacute rejection of such allografts in humans [Rossi *et al.* 2005a]. This hyperacute immunotherapy is based on the hypothesis that reactivity against α Gal epitopes in humans can trigger immune response against cancer cells. This potent immune reaction is accountable for generating cell-mediated immunity against tumor antigens demonstrated in animal models [Rossi *et al.* 2008, 2005a, 2005b].

Hardacre and colleagues presented results of an open-label, multi-institutional phase-II study (NLG0205) [ClinicalTrials.gov identifier: NCT00569387] of algenpantucel-L with adjuvant chemotherapy with gemcitabine and 5-FU/radiation after R0/R1 resection [Hardacre *et al.* 2012]. In this study 69 out of 73 patients were evaluable and they received 100 million cells ($N = 43$) or 300 million cells ($N = 26$) injected intradermally in up to 14 vaccinations. No serious adverse events were attributed to the immunotherapy. The most common adverse event was induration and pruritus at the site of immunization. These skin manifestations self-resolved typically within a week. Interestingly; eosinophilic infiltrates at the injection site in all tested patients was demonstrated in addition to peripheral eosinophilia that developed in 70% of patients. Of these patients, 30% showed persistent eosinophilia for up to 2 years.

The primary endpoint of this study was 1-year disease-free survival (DFS) and was reached by

62% of patients and the secondary endpoint was overall survival at 1 year, which was achieved by 86%. The results from this study compared favorably with the RTOG-9704 trial in which patients received the same chemoradiation regimen [Regine *et al.* 2008]. Despite patients participating in NLG0205 having greater lymph node involvement than the RTOG-9704 population (81% *versus* 68% positive nodes), they showed better 1-year overall survival (86% *versus* 69%). Moreover, based on the validation of the sixth edition of the American Joint Committee on Cancer Pancreatic Cancer Staging System by Bilimoria and colleagues [Bilimoria *et al.* 2007], and the prognostic criteria described by Brennan and colleagues [Brennan *et al.* 2004], the predicted 1-year overall survival for patients in NLG0205 was 55–63% compared with the observed survival of 86%, representing over 30% improvement in survival. In conclusion, algenpantucel-L showed significant survival advantage for resected pancreatic cancer with minimal associated toxicity and compared quite favorably with previously reported data.

Based upon these encouraging results a large phase III trial began in May 2010 and patients are now being enrolled at over 50 cancer centers in the USA [ClinicalTrials.gov identifier: NCT01072981].

Granulocyte-macrophage colony-stimulating factor vaccine

Immunotherapy for cancer mainly involves the autologous or allogenic tumor cells to create a systemic response. Dranoff and colleagues showed that irradiated tumor cells expressing murine granulocyte-macrophage colony-stimulating factor (GM-CSF) caused potent, long-lasting antitumor immune response which required both CD4 and CD8 T cells in B16 melanoma models [Dranoff *et al.* 1993]. GM-CSF was a potent cytokine and it was able to mobilize monocytes, eosinophils and lymphocytes to the tumor sites. In this study, GM-CSF vaccine showed tumor-free survival and also caused regression of tumor in mice. Jaffee and colleagues conducted a phase I study of irradiated, allogenic GM-CSF-transduced cancer vaccination in 14 patients with stage I, II and III pancreatic adenocarcinoma. All 14 patients received escalating doses of GM-CSF-secreting pancreatic tumor vaccine 8 weeks after the pancreaticoduodenectomy. Twelve of 14 patients received a 6-month course of adjuvant

chemoradiation [Jaffee *et al.* 2001]. Vaccination also induced delayed type hypersensitivity (DTH) response in three subjects. These three DTH responders remained disease free at more than 25 months after diagnosis. The immunotherapy was well tolerated with minor toxicities.

A single-institution, phase II study by Lutz and colleagues was conducted in patients with pancreatic cancer who were treated with GM-CSF-transduced allogenic whole-cell line pancreatic adenocarcinoma immunotherapy after pancreatic tumor resection followed by chemoradiation (5-FU continuous infusion with concurrent chemotherapy). Sixty patients were enrolled of a total 83 screened patients. The primary reason for exclusion was disease recurrence as determined by postsurgical clinical evaluation primarily based on CA19-9 elevations, computed tomography scans and elevated liver enzymes. Therapy was well tolerated and no dose-limiting toxicities were observed. A total of five immunotherapy treatments were delivered intradermally and the first treatment was given 8–10 weeks after surgical resection. The results showed that the DFS at 1 year was 67% and the survival at 1 year was 85% [Lutz *et al.* 2011]. The most common adverse event was erythema, induration or pain at the vaccine site which was self limiting. This immunotherapy-induced mesothelin-specific CD8 T cells in human leukocyte antigen (HLA)-A1+ and A2+ patients which correlated with DFS.

Early studies have shown the effect of GM-CSF vaccine in patients with resected pancreatic adenocarcinoma and it demands further investigation in stage II/III and in advanced or metastatic disease. Clinical trials currently enrolling patients with pancreatic cancer for vaccines include the following: a Safety and Efficacy Trial of Vaccine Boosting With Lethally Irradiated Allogeneic Pancreatic Tumor Cells Transfected With the GM-CSF Gene for the Treatment of Pancreatic Adenocarcinoma [ClinicalTrials.gov identifier: NCT01088789]; a Phase II, Randomized, Multicenter, Open-Label Study of the Efficacy, Immune Response of the Sequential Administration of GVAX Pancreas Vaccine Alone or Followed by CRS-207 in Adults With Metastatic Pancreatic Adenocarcinoma [ClinicalTrials.gov identifier: NCT01417000]; a Randomized Three-arm Neoadjuvant and Adjuvant Feasibility and Toxicity Study of a GM-CSF Secreting Allogeneic Pancreatic Cancer Vaccine Administered Either Alone or in Combination With Either a Single

Intravenous Dose or Daily Metronomic Oral Doses of Cyclophosphamide for the Treatment of Patients With Surgically Resected Adenocarcinoma of the Pancreas [ClinicalTrials.gov identifier: NCT00727441].

Peptides and DNA vaccines

Ras

K-Ras mutations are found in up to 90% of the pancreatic cancers [Almoguera *et al.* 1988]. Mutant K-ras is exclusive to cancer cells and is not present in normal cells. These point mutations can be recognized both by helper T cells and cytotoxic T cells [Abrams *et al.* 1997]. This led to the first peptide vaccine in human trials targeting K-ras mutant pancreatic cancer which showed that this vaccine was safe [Gjertsen *et al.* 1995]. In a Norwegian phase I/II study, synthetic ras-peptide cancer vaccine was evaluated for safety in five patients with unresectable pancreatic cancer [Gjertsen *et al.* 1996]. The induction of immune response was seen in two out of five patients and the vaccine was well tolerated. Subsequently, another study evaluated the mutant p53- and K-ras-derived peptides in 39 patients with several types of cancer, including pancreatic cancer, and showed tolerable safety and inducible immune response [Carbone *et al.* 2005]. Only one of nine patients with pancreatic cancer showed cytotoxic T-cell response. A phase I/II clinical trial of synthetic mutant ras peptides with GM-CSF was conducted in 48 patients (10 were surgically resected and 38 had advanced disease) and showed induction of peptide-specific immunity in 25 out of 43 evaluable patients [Gjertsen *et al.* 2001]. Patients with advanced cancer with immune response to the vaccine showed prolonged survival compared with nonresponders (148 days *versus* 61 days respectively). Long-term 10-year follow up of this study and a subsequent study of 23 patients who received peptide vaccine after surgical resection of pancreatic cancer showed improved survival and long-term immune response. Median survival for the 20 evaluable patients was 27.5 months, with 17 of 20 patients responding immunologically to the vaccine. The 5-year survival of 20 patients was 22% and 29% for 17 patients with immune response. At 10 years, 4 of 20 patients were alive versus 0 of 87 non-vaccinated patients. The treatment had minimal side effects at the 10-year update.

Recently, another study evaluated the ras-peptide vaccine in pancreatic cancer [Abou-Alfa *et al.* 2011]. Twenty-four patients with resected

pancreatic cancer were vaccinated with 21-mer peptide vaccine once monthly for 3 months. The median survival of all 24 patients with vaccination was 20.3 months, which is comparable to the historical data. In this study, there was no observed relationship between immune response and clinical outcome. K-ras vaccination was tolerable and safe.

Telomerase peptide vaccine

Telomerase is a ribonucleoprotein enzyme that is expressed in 85–90% of cancer cells but not in normal cells [Vasef *et al.* 1999]. Telomerase maintains telomeres which are the chromosome ends that maintain stability, and is activated in the majority of human cancer cells. Three components of human telomerase have been detected: human telomerase RNA component [Feng *et al.* 1995], human telomerase protein 1 [Nakayama *et al.* 1997] and human telomerase reverse transcriptase (hTERT), which is a telomeric catalytic subunit [Nakamura *et al.* 1997]. Counter and colleagues showed that, in humans, mRNA expression of hTERT levels are high in tumor cells parallel to the telomerase enzyme activity [Counter *et al.* 1998]. Thus by activating the mRNA subunit of hTERT and telomerase enzyme, cancer cells remain immortal. Telomerase is expressed in pancreatic cancer and is an attractive tumor antigen target for immunotherapy [Suehara *et al.* 1998].

Telomerase peptide vaccine GV1001 represents a 16-aa hTERT peptide that binds to multiple HLA class molecules. It may activate combined CD4/CD8 T-cell response and its mechanism depends on antigen-presenting cells (APCs) in the skin and their presentation to epitopes of vaccine. GV1001 was studied in a phase I/II study by a Norwegian group which showed prolonged survival and tolerability [Bernhardt *et al.* 2006]. In this study, 48 patients with unresectable pancreatic cancer were given intradermal injection of telomerase peptide at three dose levels (60, 300 and 1000 nmol) along with GM-CSF for 10 weeks followed by optional monthly booster vaccines. Delayed-type hypersensitivity and *in vitro* T-cell proliferation were also measured. Of the 27 evaluable patients, median survival for the intermediate dose group of 300 nmol was 8.6 months, which is significantly longer than the low- and high-dose groups with a statistically significant *p* value. GV1001 vaccine was well tolerated with 1-year survival in

the intermediate dose group being 25%. Immunogenic response was correlated with prolonged survival.

The other two phase III studies with GV1001 in patients with nonresectable pancreatic cancer were Primo Vax and Telo Vac. The Primo Vax trial examined vaccine monotherapy *versus* gemcitabine but was terminated secondary to lack of survival advantage. The TeloVac trial had three arms: gemcitabine/capecitabine; sequential vaccine and gemcitabine/capecitabine; and concurrent gemcitabine/capecitabine and vaccine. This study was closed for accrual and the results are not available at this time. Another study is evaluating radiation therapy, tadalafil, sargramostim, gemcitabine and telomerase vaccine (GV1001) in patients with unresectable pancreatic cancer and is currently enrolling [ClinicalTrials.gov identifier: NCT01342224].

Carcinoembryonic antigen and mucin 1

The carcinoembryonic antigen (CEA) is an oncofetal antigen that is expressed highly in the majority of pancreatic cancers. TRICOM is a poxvirus-based vaccine containing a combination of three T-cell costimulatory molecules: B7-1, intercellular adhesion molecule 1 (ICAM-1) and leucocyte function associated antigen 3 (LFA-3). A phase I study of TRICOM with CEA vaccine was conducted in 58 patients with metastatic malignancy by Marshall and colleagues [Marshall *et al.* 2005]. In this study, CEA-TRICOM vaccine was used with or without GM-CSF and only one patient had pancreatic cancer. This patient had progressed with increasing pain and CA 19-9 on previous CEA vaccination. After two vaccinations with CEA-TRICOM, CA 19-9 and pain levels decreased for almost 1 year. This study showed that CEA-TRICOM vaccines were safe and generated significant CEA-specific immune response with associated clinical benefit. Another phase I study in advanced pancreatic cancer was conducted with poxviruses targeting CEA and mucin 1 (MUC1) [Kaufman *et al.* 2007]. Ten patients with advanced pancreatic cancer were treated with vaccine containing vaccinia virus expressing tumor antigens CEA and MUC1 with three costimulatory molecules B7.1, ICAM-1 and LFA-3 (TRICOM) (PANVAC-V) and fowlpox virus expressing the same antigens and costimulatory molecules (PANVAC-F) along with GM-CSF. Antibody response was observed in all 10 patients and T-cell response was observed in

5 out of 8 evaluable patients. A significant increase in overall survival was noted in patients who expressed anti-CEA or MUC1-specific immune responses compared with those who did not. It showed that the poxvirus vaccine is tolerable with minimal side effects and is able to generate immune responses. A phase III trial of 255 patients treated with PANVAC-VF, recombinant vaccinia and fowlpox viruses coexpressing CEA, MUC1 and TRICOM failed to improve overall survival compared with palliative chemotherapy or best supportive care.

Survivin

Survivin is a member of the inhibitor apoptosis family, which is highly upregulated in most malignancies, including pancreatic cancer [Sato *et al.* 2001]. In murine pancreatic and lymphoma models, survivin DNA vaccine showed significant slow tumor growth and longer survival compared with those vaccinated with vector DNA [Zhu *et al.* 2007]. A case report of a 77-year-old patient with metastatic pancreatic cancer refractory to gemcitabine therapy was treated with survivin-based peptide vaccination and showed partial remission (PR) in liver metastasis at 6 months and complete remission (CR) at 8 months. Immunological testing showed strong vaccine-induced immune reactivity against survivin peptide. When weaned off the vaccine while in CR, the patient developed recurrent disease [Wobser *et al.* 2006]. A recent study of a murine pancreatic model using modified vaccinia ankara (MVA) along with gemcitabine showed enhanced survivin-specific CD8 interferon (IFN)- γ immune responses in MVA-survivin immunized mice [Ishizaki *et al.* 2011]. The synergistic effect of chemo-immunotherapy needs to be further tested.

Antigen-pulsed dendritic cells

DCs are the most potent APCs that are capable of priming naïve T cells and can stimulate memory T cells and B cells to generate antigen-specific response. DC-based immunotherapy with gemcitabine or S-1 was given in 49 patients with advanced pancreatic adenocarcinoma [Kimura *et al.* 2012]. Vaccine was given as a DC vaccine alone or a DC vaccine with lymphokine-activated killer (LAK) therapy. Median survival in these patients was 360 days. Patients receiving DC vaccine along with chemotherapy and LAK cell therapy had prolonged survival compared

with patients who received DC vaccine and chemotherapy. Of all 49 patients, 2 had CR, 5 had PR and 10 had stable disease. The authors concluded that DC-based vaccine therapy with chemotherapy was shown to be safe and may induce responses.

Carcinoembryonic antigen

CEA is highly expressed in pancreatic cancers. Autologous monocyte-derived DCs loaded with the mRNA-encoding CEA was given to three patients with resected pancreatic adenocarcinoma after neoadjuvant chemoradiotherapy for 6 months [Morse *et al.* 2002]. The immunization was well tolerated without toxicity except for local injection site reaction. All patients were alive without evidence of disease more than 2½ years after the diagnosis.

Mucin 1

MUC1 is a specific pancreatic cancer protein that is highly expressed on the surface of pancreatic cancer cells [Kotera *et al.* 1994]. Previously, a phase I/II trial of mucin gene transfected DC vaccine showed an increase in frequency of mucin-specific IFN-secreting CD8 cells, suggesting an immune response in 4 of 10 patients [Pecher *et al.* 2002]. In a phase I study of 16 patients with advanced pancreatic cancer, who were vaccinated with DCs pulsed with MUC1, the patients showed an increase in CD8 cells in peripheral blood after vaccination. Two of 15 patients with resected pancreatic cancer were alive and disease free at 32 and 61 months [Ramanathan *et al.* 2005]. Recently, a phase I trial of pulsed human DCs from the peripheral blood of patients with advanced pancreatic cancer with a MUC1 peptide was conducted by Rong and colleagues [Rong *et al.* 2012]. Seven patients were enrolled; six of these patients had metastatic disease and one had stage III pancreatic cancer. All patients underwent apheresis for culturing DCs and it was pulsed with MUC1. Vaccine administration was not associated with significant toxicity or autoimmunity. In response to MUC1-peptide vaccination, IFN γ and granzyme B production by peripheral blood mononuclear cells (PBMCs) and antigen reactivity in PBMCs was observed. There was no significant clinical benefit except for resolution of back pain in one patient. This phase I trial showed that the MUC1-peptide-pulsed vaccination was feasible and these findings

need further investigation to translate into clinical efficacy.

Heat shock protein–peptide complex

Heat shock protein (HSP), a component of HSP–peptide complex (PC), works as a peptide chaperone for stabilizing and delivering peptides. HSP is a family of proteins expressed in all species, induced by stress. They are classified into different subtypes like HSP 110, 90, 60 and 28 according to the molecular weight. HSPs are presented within HLA class I complex on the cell surface. HSPPC-96 is the first autologous HSP-based vaccine, produced from the tumor tissue of the resected specimen from the patient. In animal studies, tumor-derived HSPPC has been shown to induce immunity against autologous tumors [Oki and Younes, 2004]. A phase I pilot trial of patients with resected pancreatic cancer who received no adjuvant radiation or chemotherapy showed feasibility of preparing HSPPC-96 from the resected tumor [Maki *et al.* 2007]. A total of 10 patients were vaccinated with 5 µg of autologous HSPPC-96 weekly for four doses. No dose-limiting toxicities were observed. There was no correlation between survival and immune response. Three of 10 patients were alive without disease at 2.6-, 2.7- and 5-year follow up. This study showed that vaccine preparation from resected tumor and administration were feasible. Further studies need to evaluate the clinical efficacy of HSP vaccines in patients with pancreatic cancer.

Discussion

Pancreatic cancer remains a deadly disease with very few treatment regimens showing meaningful improvement in survival. Immunotherapy for pancreatic cancer seems promising with less toxicity. Hardacre and colleagues presented highly encouraging results of a phase II multicenter study of algenpantucel-L with adjuvant chemotherapy with gemcitabine and 5-FU/radiation after R0/R1 resection [Hardacre *et al.* 2012]. DFS at 1 year was 62%. Adjuvant algenpantucel-L in patients with high-risk, surgically treated pancreatic cancer resulted in 1-year survival of 86%. This demonstrates an improvement of 37% over predicted 1-year outcome based on nomogram analysis of this same group of patients on RTOG 9704 [Regine *et al.* 2008]. Based on these results a large phase III multicenter randomized study is actively enrolling patients for the

treatment of resected pancreatic cancer. GV1001 vaccine therapy has shown good tolerability in phase I/II trials. Other vaccine therapies including survivin vaccine, ras peptide, HSP and others have shown promising responses in phase I or II trials of patients with resected pancreatic cancer in the adjuvant setting. In a single-center phase II study, GM-CSF vaccine showed encouraging results when given after resection followed by chemoradiation [Lutz *et al.* 2011]. GM-CSF vaccine treatment was well tolerated with minimal side effects. These data need to be tested in phase III trials to see whether the results can be translated into meaningful gains in survival and can be reproduced in larger populations.

To date, there is no vaccine therapy showing benefit in metastatic pancreatic cancer. One case of a 77-year-old patient who was treated with survivin-based peptide vaccination had PR in liver metastases at 6 months and CR at 8 months [Wobser *et al.* 2006]. However, the patient developed recurrent disease after weaning the vaccine therapy. Other than a few cases, vaccine therapy has not shown benefit in metastatic pancreatic cancer.

Gemcitabine was the standard of care for a decade prior to FOLFIRINOX and in patients with poor performance pancreatic cancer. The treatment for good performance metastatic disease has been FOLFIRINOX [Conroy *et al.* 2011] which showed impressive efficacy and substantial side-effect profile. In this study, the median OS was 11.1 in the FOLFIRINOX arm compared with 6.8 months in the gemcitabine arm. Another combination regimen of gemcitabine, docetaxel and capecitabine (GTX) has shown promising survival advantage in patients with locally advanced and metastatic pancreatic cancer [De Jesus-Acosta *et al.* 2012]. In this study, overall median OS was 11.6 months and median OS for metastatic and locally advanced pancreatic cancer in the first-line setting was 11.3 and 25 months respectively. Combining immunotherapy with these combination regimens might prove beneficial in patients with metastatic pancreatic cancer.

Immunotherapy was found to be well tolerated with minimal toxicities. Vaccine therapy is being tested in early phase clinical trials. Table 1 summarizes clinical trials currently in progress. Most immunotherapy studies have been performed in the adjuvant setting, in which the expected survival is already moderate. Other check point

Table 1. Vaccine trials in progress.

Investigator/center	Stage	Study phase	Vaccine	Antigen
Multicentered	Resected Stage I and II	III	Algenpantucel-L	Genetic modification expressing α Gal epitope pancreatic cells
Le, Dung / John Hopkins	Metastatic	II	GVAX and CRS-207	Whole cell and mesothelin
Laheru, Daniel / John Hopkins	Stage I or II	II	GVAX	Whole cell GM-CSF vaccine with cyclophosphamide
Zervos, Emmanuel/ East Carolina	Locally advanced or low volume metastatic	II	Dendritic cell	Autologous dendritic cell vaccine $\pm$ radiation
Le, Dung / John Hopkins	Locally advanced and metastatic	Ib	Allogenic tumor vaccine + GM-CSF	Vaccine $\pm$ ipilimumab
Gotoh, Mitsukazu/ Fukushima	Locally advanced, recurrent and metastatic	I	Angiogenic peptide vaccine	VEGFR1/2 epitope with gemcitabine
Poplin, Elizabeth/ UMDNJ	Locally advanced and metastatic	I	PANVAC	Fowlpox vaccine with recombinant GM-CSF

α Gal, galactosyl; GM-CSF, granulocyte-macrophage colony-stimulating factor; UMDNJ, University of Medicine and Dentistry, New Jersey; VEGF, vascular endothelial growth factor.

inhibitors like cytotoxic T-lymphocyte antigen 4 and programmed death 1, which have shown benefit in melanoma or lung cancer, also need to be evaluated in pancreatic cancer. A phase II study of ipilimumab in 27 patients with locally advanced and metastatic pancreatic cancer showed no survival advantage, but one of these patients had delayed clinical response [Royal *et al.* 2010]. These combination trials need further exploration of who could benefit from these immunotherapies, thus getting us closer to ‘personalized medicine’.

Conclusion

Immunotherapy has the potential to treat minimal residual disease after pancreatic resection, and larger phase III trials are currently underway. These trials might confirm a significant clinical benefit with minimal added toxicity. In addition, future studies of metastatic and nonresectable pancreatic cancer treatment are needed. A combination of chemotherapy treatments with immunotherapy has shown promising results and further evaluation in larger trials is encouraging. As more biological targets and mechanisms are being discovered, additional evaluation of how to enhance the efficacy of immunotherapies and augment the immune-elicited responses is needed in the near future, including check

point inhibition and more complex combination trial designs.

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Conflict of interest statement

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