Review Article

Vaccine Therapy for Pancreatic Cancer: As a Novel Therapeutic Approach?

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Abstract

Pancreatic cancer is one of the deadliest human malignancies and little progress has been achieved in its treatment over the past decades. Historically, chemotherapy or radiotherapy did not provide significant survival benefit in advanced pancreatic cancer. Thus, new therapeutic approaches are needed. As there is strong evidence that pancreatic cancer elicits antitumor immune responses, scientists have tried to stimulate the antitumour activities of the immune system to fight against pancreatic cancer, but has not reached to expected result. Pancreatic cancer activates both antitumor immune responses and immunosuppressive mechanisms leading to tumor development and progression. This action is achieved through mobilization and activation of immune suppressive cells (CAFs), tolerogenic DCs, MDSCs, TAMs, Treg cells and cancer cells-derived soluble factors that promote the induction of tolerance through the generation of CD4+α chain of IL-2R (CD25)+ fork head box P3 (Foxp3) subset. Vaccine therapy relies on the administration of biological preparations that include an antigen that is specifically expressed by malignant cells, boosting the natural ability of the immune system to react against neoplastic cells. Potent vaccines stimulate antigen presentation by dendritic cells, hence driving the expansion of antigen-specific effector and memory T cells. In this paper we analyze recent preclinical and clinical efforts towards vaccine therapy for pancreatic cancer designed to target pancreatic cancer-associated antigens and to elicit an antitumor response in vivo.

ABBREVIATIONS

Pancreatic cancer-PC ; 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin-FOLFIRINOX; Myeloid-derived suppressor cells – MDSC; T regulatory cells- Treg ;Tumor microenvironment –TME; Tumor associated macrophages-TMAs; Natural killer Cells- NK cell; Cytotoxic T lymphocyte –CTL; Granulocyte-macrophage colony-stimulating factor- GM-CSF; Tumor associated antigens-TAAs; Dendritic cell- DCs; Human leukocyte antigen –HLA; Major histocompatibility complex -MHC; C-phosphate-G – CpG.

Core Tip: This article includes vaccine therapy strategy for pancreatic cancer and different immunogenic obstacles due dysfunctional immune system in PC leading to tumor development, tumor progression, and resistance to therapy.

INTRODUCTION

Pancreatic Cancer (PC) is the fourth leading cause of cancer death in United States and seventh in China, with 45,220 new cases in 2013 and estimated 38,460 deaths in the USA [1,2]. Treatment of PC has become multimodal with chemotherapy, radiation and surgical resection in the hope of long term survival. The only chance for cure and long -term survival is microscopic negative margins with R0 surgical resection [3]. However, only 10% to 20 % of patients with PC have resectable disease at the time of diagnosis, approximately 30 to 40 percent have locally advanced tumor and another 40 percent will have metastatic disease at the time of diagnosis, [1,4] and thus palliative chemotherapy remains the only option for most of these patients [5]. The overall five-year survival probability is less than 5% for all stages combined [1,3,4,6]. Even with advancement in surgical techniques most of the patients undergoing complete surgical resection experience a recurrence [7]. Several autopsy studies suggest that 8%–15% of PC patients die with locally advanced disease and without metastatic spread [8].

There are only a few chemotherapeutic agents that have shown to be effective against PC to date, such as FOLFIRINOX regiment and more recently combination of gemcetabine and erlotinib has shown somehow better result in treatment of PC [9,10]. The survival benefits for patients treated with these regimens are marginal and hence we are in urgent need of novel therapeutic approaches against PC.

As in recent years researchers has grown deeper

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understanding in the field of cancer immunology and their antigens that have given great hope for new alternative treatments for a variety of solid tumors including PC. Emerging evidence supports a critical role for the immune system in PC tumor development, progression and eradication [11,12]. There is strong recent evidence that classical anticancer treatments heavily rely on the immune system for their effectiveness [13-15]. Desmoplasia and the Tumor Microenvironment (TME) are increasingly seen as major contributors to chemoresistance in PC [16]. Studies has shown that Tumor Associated Macrophages (TMAs) can influence the response of cancer cells to chemotherapy in the context of a process known as environment-mediated drug resistance [17,18]. Targeting specific immunotherapy could be revolutionary step in the treatment of PC. In support of the PC-specific immunotherapy approaches there are many data showing PC patients generates B and T cells specific to antigens expressed on autologous pancreatic tumor cells [19-21] . Antigens expressed in PC cell such as Carcinoembryonic Antigen (CEA) (over 90%), [22] wilms' tumor gene 1 (WT1) (75%), [23] mucin 1 (MUC1) (over 85%), [24] survivin (77%), [25] human telomerase reverse transcriptase (hTERT) (88%), [26] HER-2/neu (61.2%), [27] p53 (67%), [28] mutated K-RAS (73%) [29] and α-enolase [30] can be potential targets for immunotherapy. This review summarizes clinical and preclinical efforts towards vaccine strategies and clinical trials for PC.

Dysfunctional immune system in PC-tumor development and progression

It has been found that dysfunctional immune system in PC has a critical role for the development and progression of tumor [11,12]. It is known that both the innate and the adaptive immune system are active against human cancers [31]. However, cancer cells escape the innate and adaptive immune responses (immunosurveillance) by immunoselection (selection of nonimmunogenic tumor cell variants, also known as immunoediting) or immunosubversion (active suppression of the immune response) [32]. Anticancer function of the immune system is achieved by cytotoxic CD8 T cells, T helper-1 (Th1) cells, mature Dendritic Cells (DCs), activated pro-inflammatory macrophages (M1) and NK cells [33]. Under the tumor induced immunosuppressive environment T helper cells acquire a T helper cell type 2 phenotype (Th2), which does not support cytotoxic CD8 T cell responses and is resistance toward tumors, macrophages (M1) switch to the immunosuppressive M2 state [34], In addition, the environment in pancreatic cancer is consist of not only cancer cells but also immune suppressive cells such as Cancer-Associated Fibroblasts (CAFs), tolerogenic DCs, Myeloid-Derived Suppressor Cells (MDSCs), immunosuppressive Tumor-Associated Macrophages (TAMs), and T regulatory cells (Treg cells) which inhibit effector immune responses [35]. There are increasing evidences that cancer cells-derived soluble factors promote the induction of tolerance through the generation of CD4+α chain of IL-2R (CD25)+ forkhead box P3 (Foxp3)+ Treg subset, which is linked to compromised antitumor immune responses [36]. Pancreatic cancer cells modulate the immune system and avoid detection by effector immune by production of immune suppressive cytokines (e.g., TGF-β, IL-10, and IL-6), by expressing surface molecules that mediate immune suppression (e.g., Vascular Endothelial Growth Factors (VEGF$_s$), Fas Ligand

(Fas-L), Programmed Death-1 Ligand (PD-L1), indolamine-2, and 3-dioxygenase (IDO), [35] and interference with MHC class I peptide presentation by down-regulation of MHC class I expression or disabling of the antigen degradation or antigen insertion into the MHC class I [34]. Thus, leading to tumor progression.

Cancer vaccines strategies

What determines whether cancer vaccines can become a success in human immunotherapy? Exactly the same as required for infectious diseases, cancer has to be immunogenic and activate cytotoxic T cell responses. Consequently, cancer cells have to possess immunogenic antigens susceptible of being targeted by vaccination. Cancer vaccines are biological preparations that involve administering a tumor antigen with the aim of stimulating tumor-specifc immunity. Antigen can be delivered by number of ways in form of wholecell recombinant vaccines, Dendritic Cell (DC) vaccines that combine antigen with DCs to present to white cells, DNA vaccine by inserting viral, bacterial or Yeast DNA into human or animal cells, or T-cell receptor peptide vaccines by inserting peptides to modulate cell-mediated immunity. To be considered an ideal tumor vaccine candidate, expression of the antigen must be restricted to the tumor or only minimally expressed elsewhere in the body. Vaccination against tumor antigens is an attractive approach to adjuvant treatment after surgery, when tumor-induced immune suppression is minimal [37]. Cancer vaccines were first approved for hepatocellular carcinoma and cervical cancer prevention. More recently, the first vaccine (Sipuleucel-T, Provenge) was approved for the treatment of hormone refractory prostate cancer [38].

Compared to all other standard modalities (surgery, chemotherapy, radiotherapy, and adaptive immunotherapy), an effective vaccine-based immune response against tumor may be the only cancer treatment with the potential benefit to last a lifetime. Theoretically, vaccinated patients could mount an immune response able to either cure tumor or keep it under constant restraint (i.e., immune surveillance), delaying tumor recurrence and prolonging survival.

For the development of efficient vaccine researchers have been using different strategies such as:

- Cancer vaccine should seek for Tumor specific antigens and distinct from self-proteins.

- Selection of the appropriate adjuvant, molecules that activate antigen-presenting cells to stimulate an antigen specific cytotoxic T lymphocyte (CTL) mediated immune responses [39].

- Effective vaccine should seek to provide long term memory to prevent tumor recurrence which can activate both innate and adaptive immune system [40].

- Efforts towards improving the clinical efficacy of immune therapy should involve strategies to neutralize or overcome immune suppression.

VACCINES FOR PANCREATIC CANCER

Several vaccine therapy strategies are being actively tested in clinical trials. An over view of clinical trials in provided in Table 1.

Peptide vaccines

Peptide-based cancer vaccines are preparations made from antigenic protein fragments (called epitopes), that represent the minimal immunogenic region of antigens [41,42], designed to enhance the T cell response, especially the CD8+. Induction of CTLs needs peptides derived from TAAs to be presented on the surface of APCs (antigens presenting cells), such as DCs, in the context of HLA molecules.

KRAS vaccines: The association of mutant Kras with pancreatic cancer was established two decades ago [43,44]. The most common activating point mutation involves the KRAS2 oncogene, on chromosome 12p, in over 90% of PC [45]. This is the highest fraction of K-ras alteration found in any human tumor type. Recent tumor genome sequencing studies have established the prevalence of mutant Kras in Pancreatic Intraepithelial Neoplasia (PanINs), the most common precursor lesions and in pancreatic cancer with increased precision [46-48].In a Phase I/II study, the administration of synthetic KRAS-derived peptides to un resectable pancreatic cancer patients resulted in an immune response in 2 out of 5 individuals [49]. Since native epitopes have relatively low immunogenicity, granulocyte-macrophage colony-stimulating factor (GM-CSF) was applied to achieve efficient vaccination in the study. Among 48 patients with pancreatic cancer (10 surgically resected and 38 with advanced disease), vaccination of mutant K-ras peptides in combination with GMCSF resulted in immune responses and prolonged survival [50]. Moreover, another group also reported that vaccination of 24 patients with resected pancreatic cancer with K-ras peptide in combination with GM-CSF proved to be safe without tumor regression and Median recurrence-free survival time was 8.6 mo and median overall survival time was 20.3 mo [51].In one clinical study vaccination with mutated K-ras resulted in 20% long term survivors [52]. A randomized phase II placebo controlled trial using recombinant mutated K-ras protein for vaccination in combination with gemcitabine, in patients with resected pancreatic cancer, is currently ongoing [53]. Lisiansky selectively kill Ras-transformed cells by over expressing the pro-apoptotic protein, p53 upregulated modulator of apoptosis (PUMA) under a Ras-responsive promoter, and assess it may become a useful, effective and safe approach to selectively target Ras-mutated tumor cells [54].

Survivin vaccines: Survivin is a member of the inhibitor apoptosis family, which is highly upregulated in most malignancies, including pancreatic cancer [55]. In a study, murine pancreatic and lymphoma models, survivin DNA vaccine showed significant slow tumor growth and longer survival compared with those vaccinated with vector DNA [56]. In a study, a survivin-derived peptide (AYACNTSTL) was used in combination with IFN α to vaccinate six patients who had advanced pancreatic cancers. Tetramer and enzyme-linked immunosorbent spot (ELISPOT) assays revealed that more than half of the patients had manifested immunological responses to vaccination, which were often accompanied by clinical benefits [57]. However, this vaccine still need to be tested in a large population.

Gastrin vaccines: Gastrin and cholecystokinin B receptor (CCKBR, also known as CCK-2) are upregulated and co-expressed in both pancreatic cell lines and human PDA specimens and have been implicated in autocrine, paracrine, and endocrine growth pathway [58]. In a randomized, double-blind, placebo-controlled, group-sequential multicenter trial of G17DT in patients with advanced pancreatic cancer unsuitable for or unwilling to take chemotherapy, resulted in a nearly 2-fold increase in median overall survival, as compared with placebo (151 vs. 82 d, respectively; p = 0.03). Anti-gastrin immune responses were noted in 73.8% of the patients and correlated with longer overall median survival versus non responders and placebo (176 vs. 63 vs. 83 days respectively, p = 0.003) [59]. Gastrin-based vaccines appear therefore to be well tolerated by and could represent a new therapeutic option for pancreatic cancer.

HSP-peptide complex vaccines: Heat Shock Protein (HSP), a component of HSP–Peptide Complex (PC), works as a peptide chaperone for stabilizing and delivering peptides. HSP-peptide complexes can be presented on MHC class I molecules on the cell surface. Tumor-derived HSP-peptide complexes have been shown to induce antitumor immune responses in preclinical studies. HSP96-peptides complexes produced from resected tumor tissues were the first to be employed in anticancer vaccines. A phase I pilot trial of patients with resected pancreatic cancer who received no adjuvant radiation or chemotherapy showed feasibility of preparing HSPCC-96 from the resected tumor. 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, exhibiting a median overall survival of 2.2 years. Three of 10 patients were alive without disease at 2.6, 2.7 and 5-years follow up [60]. 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.

WT1, cancer-testis antigens (CT) and VEGFRs vaccines: Wilms Tumor gene (WT1) protein is an attractive target for cancer immunotherapy, in a study of 32 patients with advanced pancreatic cancer was treated with WT1 vaccine in combination with gemcitabine and was well tolerated. The association between longer survival and positive delayed-type hypersensitivity to WT1 peptide was statistically significant, and longer survivors featured a higher frequency of memory-phenotype WT1-specific cytotoxic T lymphocytes both before and after treatment [61]. Median survival time and 1-year survival rate were 8.1 months and 29% respectively.

The cancer-testis (CT) antigens are expressed by tumors of different histological types at varying frequencies (10-40%) [62]. CT antigens are absent in normal somatic cells in humans and rodents but expressed only in male germ cells (such as spermatogonial stem cells, spermatogonia, spermatocytes, spermatids and spermatozoa) during spermatogenesis in the testis (but not Sertoli and/or Leydig cells) [63-68]. Fifty two percentage of the analyzed pancreatic cancer tissue expressed at least one CT antigen [69]. Recently, in a Phase I clinical trial for advanced pancreatic cancer to investigate the safety, immunostimulatory effects, and antineoplastic activity of a multi-target vaccine composed of four distinct peptides derived from cancer-testis (CT) antigens and vascular endothelial growth factor receptors (VeGFrs) was well-tolerated, and no grade 3 or 4 adverse was observed [70]. The median overall survival (OS) of this cohort was 207 days.

Table 1: Vaccine therapy related clinical trials in pancreatic cancer.

Vaccine	Targeting Vaccines	Phase	Study year and Investigators	Number of Pt and Stage of Disease	Name of Antigen	Adjuvant therapy	Result
Peptide Vaccine	KRAS vaccines	I/II	Gjertsen MK, [49]	5 patients with histologically confirmed PC	Mutated K-ras		Resulted in an immune response in 2, showed longer survival
			Gjertsen MK, [50] Weden S [52]	48 patients ,10 Surgically resected pts and 38 pts with advanced disease	Mutated K-ras	GM-CSF	Peptide-specific immunity in 58% of pts. Responders median survival 148 vs 61 days for non-responders. 20% long term survivors
			Abou-Alfa GK, [51]	24 patients with resected PC	Mutated K-ras	GM-CSF	Median recurrence free survival 8.6 months; Median overall survival 20.3 months
		II	Estimated Study Completion Date: 2014 [53]	100 Patients following resection	Mutated K-ras	Gemcitabine	Ongoing
	Gastrin vaccines		Gilliam AD, [59]	154 patients with advanced PC, unwilling or unable to take chemotherapy	Gastrin (G17DT) versus placebo		151 days G17DT vs. 82 days placebo p=0.03
	HSP-peptide complex vaccines	I	Maki RG [60]	10 patients with resected PC	HSPCC-96		Median overall survival was 2.2 years
	WT1 vaccine		Nishida S, [61]	32 patients with advanced pancreatic cancer	WT1	Gemcitabine	Median survival time and 1-year survival rate were 8.1 months and 29%
	cancer-testis antigens (CT) vaccine	I	Okuyama [70]	9 patients with advanced pancreatic cancer	CT and VEGFRs		The median overall survival (OS) was 207 days.
	VEGFRs vaccine	I/II	Gotoh M [71]	17 Unresectable, recurrent or metastatic patients	VEGF-R1 VEGF-R2	Gemcitabine	Completed, result not reported yet
	(hTERT) vaccine	I/II	Bernhardt SL [72]	48 patients with nonresectable PC	Telomer-ase	GM-CSF	24/38 With immune responses. Induction of immune response correlated with improved survival
		III	Buanes T [73]	178 patients with advanced PC	Telomer-ase	Gemcitabine	No overall survival benefit
		I	Crocenzi T [74]	11 patients with Locally Advanced PC	Telomer-ase	tadalafil	Ongoing
	Her2/neu vaccine	I	Morse M [75]	12 patients with Her2/neu overexpressing tumors, including PC	Her2/neu		Ongoing

Recombinant Vaccines	MUC-1 and CEA in poxvirus	TRICOM, MUC-1 and CEA in poxvirus with GM-CSF	III	Arlen PM [79]	255 Metastatic pts following gemcitabine failure	MUC-1, CEA	TRICOM,GM-CSF	No overall survival benefit
	Listeria vaccines	Live attenuated Listeria vaccine (aNZ-100) vs Live attenuated mesothelin expressing Listeria vaccine (CrS-207)	I	Le DT [80]	28 patients with mesothelioma, lung, pancreas, or ovarian cancer liver metastasis	Mesothe-lin		37% of patients in CrS-207 arm live after 15 months
		Lethally irradiated genetically engineered allogeneic whole tumor and listeria	II	Le DT [81]	90 Pts with metastatic disease	Mesothe-lin and whole tumor	GM-CSF secreting allogeneic PC cells and cyclophosphamide	Ongoing
Antigen pulsed DCs vaccines		MUC-1 pulsed (DCs) vaccines	I/II	Lepisto AJ [82]	12 Pts with surgically resected pancreatic (10 pts) or biliary (2 pts) cancer	MUC-1		4 Out of 12 pts alive at 4 years
		LAK cell pulsed (DCs) vaccines		Kimura Y [83]	49 patients with unrecetable PC (Stage III,, IVa, IVB)	LAK	gemcitabine or S-1	Median overall survival of patients receiving DC vaccine and chemotherapy plus LAK cell therapy was longer than those receiving DC vaccine in combination with chemotherapy but no LAK cells
Whole tumor cell vaccines		Algenpantucel-L	II	Hardacre JM [84]	70 patients with resected PC	whole tumor	algenpantucel-L with chemotherapy (gemcitabine and 5 FU)+ radiotherapy	12-month disease-free survival was 62 %, and the 12-month overall survival was 86 %
		Algenpantucel-L	III	Multicentered [85]	722 patients with resected PC (stage I,II)	whole tumor	algenpantucel-L with chemotherapy (gemcitabine and 5 FU)+ radiotherapy	Ongoing
		Allogeneic GM-CSF	I	Jaffee EM [86]	14 patients with resected PC	whole tumor	GM-CSF vaccine with chemoradio-therapy	3 patients disease free at least 25 months after diagnosis
			II	Lutz E [87]	60 patients with resected PC	whole tumor	GM-CSF vaccine with chemotherapy (5FU) and radiotherapy	disease free survival of 17.3 months and an overall survival of 24.8 months
			II	Laheru DA [88]	60 patients with resected PC	whole tumor	GM-CSF secreting allogeneic PC cells, cyclophosphamide and cetuximab	Completed, result not reported yet
			II	Laheru DA [89]	56 Pts with resected PC	whole tumor	GM-CSF secreting allogeneic PC cells	Ongoing
			II	Laheru DA [90]	87 patients with resected PC	whole tumor	GM-CSF secreting allogeneic PC cells and IV vs oral metronomic cyclophosphamide	Ongoing
			I	Herman J [91]	18 Pts with resected PC	whole tumor	GM-CSF secreting allogeneic PC cells and cyclophosphamide followed by localized radiation (SBRT) and FOLFIRINOX	Ongoing

PC: Pancreatic Cancer; FOLFIRINOX: 5-Fluorouracil, Leucovorin, Irinotecan and Oxaliplatin; GM-CSF: Granulocyte-Macrophage Colony-Stimulating Factor; DCs: Dendritic Cell; CEA: Carcinoembryonic Antigen; MUC-1: Mucin 1; LAK: Lymphokine Activated Killer; hTERT: Telomerase Teverse Transcriptase; Her2/neu: Human Epidermal Growth Factor Receptor 2; VeGFrs: Vascular Endothelial Growth Factor Receptors; WT1: Wilms Tumor Gene; HSP: Heat Shock Protein

Two vascular endothelial growth factor receptors (VeGFrs) peptide vaccine studies using VEGF-R1 and VEGF-R2 are completed but have not reported results yet [71].

Telomerase reverse transcriptase (hTERT) and Her2/ neu vaccines: Telomerase reverse transcriptase (hTERT) is a highly immunogenic antigen and has been the target in several vaccination studies. A small phase I/II study in patients with pancreatic cancer showed T cell responses in 63% of vaccinated patients, and prolonged survival in patients exhibiting T cell responses [72]. However, a large phase III study failed to show a survival benefit in pancreatic cancer [73]. Another study is evaluating radiation therapy, tadalafil, sargramostim, gemcitabine and telomerase vaccine (GV1001) in patients with unresectable pancreatic cancer and is currently active and waiting for result [74]. Recently, vaccination against Her2/neu is also being tested in a phase I study in patients with pancreatic cancer [75].

Recombinant vaccines

Recombinant vaccines contain bacterial and viral antigen carriers thereby increasing DC activation and improving antigen presentation. They stimulate the innate immune response while efficiently recruiting and activating DCs. The most common carriers include Bacille Calmette-Guerin (BCG), Listeria Monocytogenes (LM), Salmonella and Poxviruses.

Carcinoembryonic antigen (CEA) and mucin 1 (MUC-1): The Carcinoembryonic Antigen (CEA) is an oncofetal antigen that is expressed highly in the majority of pancreatic cancers [76] and MUC-1 is a membrane bound glycoprotein known to promote pancreatic cancer epithelial to mesenchymal transition and invasiveness. It also induces CD8 T cell responses and the production of anti-MUC antibodies is associated with improved survival [77]. 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). In a phase I study of TRICOM with CEA vaccine was conducted in 58 patients with metastatic pancreatic cancer by Marshall and colleagues. 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 [78]. This study showed that CEA-TRICOM vaccines were safe and generated significant CEA-specific immune response with associated clinical benefit. In a large randomized phase-III clinical trial of 255 patients vaccination with a MUC-1 and CEA expressing viral vector showed no overall survival benefit [79].

Listeria vaccines: Listeria monocytogenes (Lm)-based vaccines stimulate both innate and adaptive immunity. In one recent study, patients bearing hepatic metastases from mesothelioma, ovarian cancer, non-small cell lung carcinoma and PC were given this L. monocytogenes strain further engineered to express mesothelin, a cell surface molecule overexpressed by a large majority of PC, mesotheliomas, ovarian cancers, and non-small cell lung carcinomas [80].Thirty-seven percent of these patients survived 15 months or more. Half of them patients were those harboring metastatic PC, and immunological analyses revealed that they had developed listeriolysin O- and mesothelin-specific T-cell responses. While a mesothelin vaccine, using genetically modified live attenuated listeria as a vector for the antigen, has also entered clinical trial [81].

Antigen pulsed Dendritic cell (DCs) vaccines

DCs are the most potent Antigen Presenting Cells (APCs) that are capable of priming naïve T cells and can stimulate memory T cells and B cells to generate antigen specific response. Antigen pulsed DCs is another vaccination strategy where patient DCs are isolated, pulsed with peptides, autologous, or allogeneic tumor lysate, or transfected with RNA, and injected back to the patients. In a study of 12 patients (10 with pancreatic cancer), where MUC-1 pulsed DCs were given as adjuvant therapy following resection, 4 of the 12 patients were alive at 4 years [82]. In the second study, a DC-based vaccine alone or combined with Lymphokine activated killer (LAK) cells was administered together with gemcitabine and/or S-1 to 49 patients with advanced pancreatic adenocarcinoma [83]. 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 complete remission, 5 had partial remission and 10 had stable disease. Thus the study concluded that DC-based vaccine therapy with chemotherapy was shown to be safe and may induce responses.

Whole tumor cell vaccines

Whole tumor cell vaccines are another strategy that has shown promise in pancreatic cancer. Autologous whole tumor cells remain a potent vehicle for generating antitumor immunity. This is because tumor cells express all relevant candidate TAAs, including both known and unidentified. Two allogeneic whole cell based anticancer vaccines are currently being investigated for their safety and antineoplastic effects in PC patients.

Algenpantucel-L: Algenpantucel-L is the most clinically advanced and promising immunotherapy for pancreatic cancer. Algenpantucel-L (also known as hyperacute-pancreatic cancer vaccine) consists an 2 irradiated, live, human allogeneic pancreatic cancer cell lines that express murine α-1,3-galactosyltransferase, which is responsible for the synthesis of α-galactosylated epitopes on cell surface proteins. Hardacre and colleagues presented the results of an open-label, multi-institutional Phase II clinical trial investigating Algenpantucel-L in combination with standard adjuvant chemoradiotherapy for the treatment of resected PC patients [84]. 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. After a median follow-up of 21 months, the 12-month disease-free survival was 62 %, and the 12-month overall survival was 86 %. The most common adverse events were injection site pain and induration. The study concluded that the addition of algenpantucel-L to standard adjuvant therapy for resected pancreatic cancer may improve survival. A multi-institutional, phase 3 study is ongoing (ClinicalTrials.gov identifier, NCT01072981) [85].

Allogeneic GM-CSF vaccine therapy: Allogeneic

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Granulocyte–macrophage colony-stimulating factor (GM-CSF) vaccine therapy, called GVAX, has been tested in a variety of early phase clinical trials. In a phase I clinical study, tumor cells, which were modified to express the immunomodulating cytokine GM-CSF, where given to 14 patients [86]. Three patients had delayed-type hypersensitivity responses to autologous tumor cells and those 3 patients had a longer disease free survival. Latter in In a phase-II study with a similar approach, 60 patients with resected pancreatic cancer were treated, yielding a disease free survival of 17.3 months and an overall survival of 24.8 months [87]. While the results did not superior result to previous study, other studies using similar approaches, or combining whole tumor vaccination with cyclophosphamide alone, or with conventional chemotherapy, are ongoing [88-91].

PERSPECTIVES

Although vaccine therapy as a single agent has encouraging results, clinical trials in PC patients have been underwhelming and disappointing. Most of these clinical studies identified a number of critical aspects that must be carefully considered for the design the next generation of cancer vaccines. As stated earlier dysfunctional immune system in PC further give rise to tumor induced immunosuppressive environment has a critical role for the development and progression of tumor. Which consist of not only cancer cells but also immune suppressive cells (CAFs, tolerogenic DCs, MDSCs, TAMs and Treg cells) and cancer cells-derived soluble factors that promote the induction of tolerance. So, novel vaccine therapy strategy should be designed for breaking immunosuppression within the tumor microenvironment, to inhibit immunologic checkpoint blockade and to modulate tumor microenvironment. Thus, this may require a combinatorial therapeutic approach which includes chemotherapy, radiation, surgery and immunotherapy.

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