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Review article

Dendritic cell-based cancer immunotherapy for pancreatic cancer

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ABSTRACT

Pancreatic cancer (PC) is a lethal disease and remains one of the most resistant cancers to traditional therapies. New therapeutic modalities are urgently needed, particularly immunotherapy, which has shown promise in numerous animal model studies. Dendritic cell (DC)-based immunotherapy has been used in clinical trials for various cancers, including PC, because DCs are the most potent antigen-presenting cell (APC), which are capable of priming naive T cells and stimulating memory T cells to generate antigen-specific responses. In this paper, we review the preclinical and clinical efforts towards the application of DCs for PC.

Introduction

Pancreatic cancer (PC) is one of the main leading causes of cancer death and has the highest fatality rate worldwide [1]. The only potentially curative therapy for PC is surgical resection [2,3]. Unfortunately, most of the time, PC is either locally advanced or metastatic at diagnosis, and as a result, the majority of PC cases are unresectable. Therefore, surgical resection can be performed in only a small number of patients [4]. Even after resection, recurrence occurs in the majority of patients, leading to a median survival of approximately 15–20 months after resection [5]. Other therapies, including radiation and chemotherapy, have limited effects in terms of increased survival because of PC cells that are resistant to chemotherapy or radiotherapy [6,7]. New treatment strategies for PC are urgently needed.

Immunotherapy has an advantage over radiotherapy and chemotherapy because it can act specifically against the tumour without damaging normal tissues [8–10]. Additionally, preclinical and clinical studies have shown that immunotherapy can induce a PC specific immune response [11–13]. Here, we review advances in dendritic cell (DC)-based immunotherapy for PC treatment.

Dendritic cells

DCs are potent antigen-presenting cells (APCs) that are highly effective in activating naive and memory T cell responses [14]. Mature DCs have a series of phenotypic and functional characteristics. They express co-stimulatory molecules, such as CD80, CD86, CD40, and CD70, which are inducible T-cell co-stimulatory ligand molecules that interact with their counter-parts, CD28, CD40L, CD27, and ICOS, respectively, which are expressed by T cells [15,16]. Additionally, DCs have elevated levels of Ag-presenting molecules, including major histocompatibility complex (MHC) class I and class II molecules [17]. For the reasons mentioned above, DCs are widely considered as the most potent APCs and are the link between innate and adaptive immunity [18,19].

DCs play a sentinel role in tumour control. They have the capacity to activate T cells (CD4+, CD8+), mutually interact with natural killer (NK) cells in tumour immune-surveillance, and directly kill tumour cells [20,21]. They can be pulsed with synthetic peptides derived from known tumour antigens, tumour-specific proteins, or tumour cell lysates; transfected with tumour mRNA, cDNA, or RNA of a specific antigen [11,22,23]; transduced with recombinant viruses [24,25]; and fused with tumour cells to induce antigen-specific polyclonal CTL responses [26]. Numerous studies have demonstrated that DCs are an ideal candidate for cancer immunotherapy and have been safe to use in human clinical trials [27–30].

Whole tumour cell- or lysate-pulsed DCs

Autologous whole tumour cells express all relevant candidate tumour-associated antigens (TAAs), including both known and unidentified antigens, which make them a potent vehicle for generating antitumour immunity. DCs have been used in tumour vaccination when pulsed with tumour lysates (TL) [31,32]. In addition

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to autologous tumour cells, allogeneic tumour cell lines can be used instead of autologous tumour cells if a patient is unresectable and other reasons [33]. Autologous DCs can process and present multiple TAAs from allogeneic tumour cells because of cross presentation in the context of appropriate MHC class I and II alleles [34].

Animal studies and tumour cell trials have shown that specific T-cell responses against tumours as well as tumour regression can be achieved when DCs are pulsed with PC cells [35,36]. The Akiyama group found that DCs pulsed with hamster pancreatic cancer cell HPD1NR lysates produced an obviously antitumour effect [37]. tumour growth was significantly inhibited by 82% in hamsters treated with TL when compared with a PBS vehicle-treated group. They found that DC or DC + TL treated hamsters had smaller disseminated tumours than the vehicle-treated hamsters. Additionally, the mean survival times in the DC + TL groups were significantly longer than in the PBS group. The anti-tumour effect of DCs pulsed with TL was strengthened when the TL was pre-heat treated, which not only led to lessened tumour size but also to a highly increased expansion of interferon (IFN)-γ-secreting T cells [38].

The safety and efficacy of DC-based immunotherapy for PC patients have been tested in clinical trials (Table 1). Stift et al. used TL-pulsed DCs to cure twenty patients (including pancreatic, hepatocellular, cholangiocellular, and medullary thyroid carcinoma cases) with stage IV disease. The generation of IFN-γpositive T cells was induced during the vaccination of three patients. Objective changes in measurable lesions or tumour markers were evident in seven patients [27]. Another trial was conducted in which a DC-based vaccine was administered to seventeen patients with refractory PC. Six patients had postoperative recurrences, and eleven were diagnosed as inoperable because of metastasis [39]. TL-pulsed DCs or TL-pulsed DCs combined with lymphokine activated killer (LAK) therapy were studied. The median survival time in these patients was 9 months. Patients receiving DC therapy conferred a significantly better survival period than LAK alone. The authors suggested that immunotherapy utilizing DC vaccination might prolong the survival of refractory PC patients.

Peptide loaded DCs

Peptide-based vaccines are preparations made from antigenic protein fragments (called epitopes), which represent the minimal immunogenic region of antigens [40,41] designed to enhance the CD8 + T cell response. The ideal TAA target should be expressed only on tumour cells or have very limited expression on normal tissues and will produce the greatest effect if it is required for tumour cell survival. Potential antigens that could be utilized for peptide-based PC immunotherapy include mucin 1 (MUC1) [42], Wilms' tumour gene 1 (WT1) [43], carcinoembryonic antigen (CEA) [44], human telomerase reverse transcriptase (hTERT) [45], HER-2/neu [46], mutant K-RAS [47], p53 [48], α-enolase [49], Mesothelin [50], MAGE-A3 [51], and survivin [52]. Comparative studies have suggested that peptide-loaded DC vaccines may elicit more cytotoxic lymphocyte (CTL) activity than peptides alone [53].

A Phase I/II clinical trial was conducted in which twelve pancreatic and biliary cancer patients, following resection of their primary tumours, were vaccinated with MUC1 peptide-loaded DCs [54]. Four of the twelve patients who were followed for over four years were alive, and they had no evidence of recurrences. A similar study was conducted by Rong et al. [55]. They used DCs pulsed with a MUC1 peptide to treat seven patients with advanced PC. The IFN-γ and granzyme B ELISPOT assay relativities significantly increased in two patients, and one patient had resolution of back

Table 1
DC-based vaccine therapy clinical trials for pancreas cancer.

DC-based vaccines	Patients	Clinical and Immunology Outcomes	Ref
TL-pulsed DCs	20 with stage IV disease, including 9 with PC	Three patients generated IFN-γ positive T cells, and 7 had objective changes in lesion measurements or tumour markers.	[27]
TL-pulsed DCs alone or TL-pulsed DCs combined with LAK	6 with recurrence PC and 11 with inoperable PC	The median survival rate was 9 months, and the DC vaccine therapy conferred a significantly better survival period than LAK alone.	[39]
MUC1-peptide loaded DC	12 with resected PC	Four of the 12 patients who were followed for over four years were alive, all without evidence of recurrence.	[54]
MUC1-peptide loaded DC	7 with advanced PC	IFN-γ and granzyme B ELISPOT assay reactivity increased significantly in 2 patients. One patient had resolution of back pain.	[55]
MUC1-peptide loaded DC	20 with unresectable or recurrent PC	One patient with multiple lung metastases experienced a complete response. Five had stable disease. The mean survival time was 9.8 months. No grade II-IV toxicity was observed.	[56]
DCs transfected with MUC1cDNA	10 with advanced breast, pancreatic, or papillary cancer	Four showed a 2- to 10-fold increase in the frequency of MUC1-specific IFN-γ-secreting CD8 + T cells. All of the PC patients in this study developed progressive disease.	[60]
DCs transfected with CEA mRNA	3 with resected PC	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.	[61]
DCs transfected with hTERT mRNA	1 with PC who could not continue chemotherapy due to sever neutropenia	The patient showed no evidence of active disease based on PET/CT scans. No serious adverse events were experienced. The patient developed an immune response against several hTERT-derived Th and CTL epitopes.	[62]
DCs engineered (secreting IL-12)	17 with several types of cancer (3 metastatic pancreatic, 5 colorectal, 9 liver)	The DC treatment induced a marked increase in infiltrating CD8 + T lymphocytes in 3 of the 11 tumour biopsies analyzed. A partial response was observed in one patient with PC.	[63]
DC-based vaccine plus LAK with gemcitabine	5 with inoperable locally advanced PC	No serious treatment-related adverse events were observed. One patient had partial remission, and 2 had long stable disease that lasted more than 6 months.	[84]
DC-based vaccine plus LAK with gemcitabine or S-1	49 with inoperable PC (Stage III,IVA, IVB)	Two had complete remission, 5 had partial remission, and 10 had stable disease. The median survival rate was 360 days.	[85]
MUC1 peptide-loaded DC with gemcitabine	42 with unresectable or recurrent PC	The median survival time was 13.9 months, and the 1-year survival rate was 51.1%. One patient had a complete response (2.4%), 3 had partial responses (7.1%), and 22 had stable disease (52.4%). The disease control ratio was 61.9%. Liver metastasis occurred in only 5 patients among 35 patients without liver metastasis before treatment.	[86]
WT1 peptide-loaded DC with gemcitabine	10 with advanced PC	Disease control, which was associated with a low neutrophil/lymphocyte ratio, was observed in all 3 patients with DTH positivity.	[87]

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