Cancer Letters 407 (2017) 57–65

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

Mini-review

PD-1/PD-L1 and immunotherapy for pancreatic cancer

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ARTICLE INFO

Article history:
Received 2 June 2017
Received in revised form
17 July 2017
Accepted 5 August 2017

Keywords:
PD-1/PD-L1
Immunotherapy
Pancreatic cancer
Immune resistance
Tumour microenvironment

ABSTRACT

Therapy that targets programmed death 1 or programmed death 1 ligand 1 (PD-1/PD-L1), which are known as immune checkpoints, has been recently rapidly developing as oncotherapy for various carcinomas. However, this therapy has a poor effect on the treatment of pancreatic cancer with PD-1/PD-L1 blockade monotherapy. In this review, the development and limitations of anti-PD-1/PD-L1 monotherapy in pancreatic cancer are discussed. We then consider the underlying mechanism of anti-PD-1/PD-L1 monotherapy failure, combination strategies overcoming resistance to anti-PD-1/PD-L1 immunotherapy and the prospect of targeting PD-1/PD-L1 for the immunotherapy of pancreatic cancer.

Introduction

Pancreatic cancer is a highly lethal human cancer, with a 7% 5-year overall survival rate [1,2]. This malignancy is the fourth and sixth leading cause of cancer-related deaths in the USA and China, respectively [1,3]. Because early diagnosis is difficult, the therapeutic efficacy is unsatisfactory, and the prognosis is poor, this lethal disease has always been an active research topic in oncological surgery. The primary therapeutic strategies include surgery and chemotherapy. However, only 20% of patients are resectable, and chemoresistance is a very common phenomenon. A growing understanding of the pathogenesis of pancreatic cancer has led to immunotherapy on the basis of stimulating and mobilizing the human immune system, and enhancing the anti-tumour capacity of the tumour microenvironment has become a research focus in the treatment of pancreatic cancer. Immunotherapy of pancreatic cancer is classified into four categories according to the different immune response mechanisms activated by neoplasms: specific active immunotherapy, specific passive immunotherapy, nonspecific adoptive immunotherapy and nonspecific immune regulation [4–6]. Therapy targeting programmed death 1 or programmed death 1 ligand 1 (PD-1/PD-L1), known immune checkpoints, has been recently rapidly developing for the oncotherapy of various carcinomas. However, the treatment of pancreatic cancer with a single PD-1/PD-L1 blockade has a poor effect. In this review, we will first primarily discuss the development and limitations of targeting PD-1/PD-L1 in the immunotherapy of pancreatic cancer. The underlying mechanism of therapy failure and the prospect of targeting PD-1/PD-L1 in the immunotherapy of pancreatic cancer will then be discussed in the latter section.

PD-1/PD-L1

PD-1, an immune checkpoint expressed by activated T cells that was supposed to be involved in the classical type of programmed cell death, was initially cloned in 1992 [7]. PD-L1 was subsequently

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http://dx.doi.org/10.1016/j.canlet.2017.08.006
0304-3835/

identified and characterized in 2000, and it has since been regarded as an immune checkpoint [8]. Tumour-associated PD-L1 was confirmed to increase T-cell apoptosis *in vitro* and *in vivo* and to protect tumour cells from being killed, which unlocked the door of T-cell-based cancer immunotherapy [9]. Additionally, various studies showed that PD-1 could suppress the excessive activation of the immune response and facilitate the maintenance of immune tolerance to self-antigens [8,10,11]. PD-1 is expressed on the surface of activated T cells after antigen recognition. However, PD-L1 is expressed by various cell types, including immune cells and tumour cells, after interaction with cytokines such as interferon (IFN)-γ, which is produced by activated T cells [10,12]. Many different human cancers can express PD-L1, including breast, urothelial, ovarian, cervical, colorectal, gastric, pancreatic and non-small-cell lung cancer, melanoma and glioblastoma [13]. PD-1 and PD-L1 (B7-H1) belong to the CD28 Ig superfamily and the B7 superfamily, respectively [14]. Preclinical studies in murine models and clinical trials have recently evaluated anti-PD-1/PD-L1 as immune checkpoint blockade therapies to overcome lethal malignancies. In addition, anti-PD-1/PD-L1 antibodies have demonstrated clinical efficacy in multiple cancer types [15,16].

PD-L1 was first considered a new predictor of prognosis for patients with pancreatic cancer in 2007, when PD-L1 upregulation in human pancreatic cancer specimens was demonstrated for the first time [17,18]. It has been suggested that a PD-L1 blockade can efficiently inhibit pre-established pancreatic cancer in a mouse model by increasing IFN-γ production and decreasing IL-10 production [14,19]. In addition, the level of tumour-infiltrating T_{regs} in PD-L1-positive tumours is higher than that in negative tumours [14]. Such outcomes provided the rationale for therapy targeting the PD-1/PD-L1 pathway against pancreatic cancer.

Immunotherapy of pancreatic cancer

In the era of personalized medicine, pancreatic cancer remains an incurable disease because an intrinsic genomic instability results in the escape of cancer cells from chemoradiotherapy or targeted therapies [20]. Because of the unsatisfactory response rates of pancreatic cancer and a tendency for resistance to current standard therapies, including surgery, radiation and chemotherapy, immunotherapy has been emerging as the fourth cornerstone of pancreatic cancer treatment, but is secondary to the previously mentioned therapeutic strategies. The relatively mild side effects of immunotherapy have quickly led the approach to become a focus of pancreatic cancer research and treatment. Additionally, it is generally accepted that the focus of treatment has changed from the tumour itself to the host immune system, mobilizing immune cells and impairing immunosuppression [20]. Immunotherapy has the greatest promise to prevent recurrence and prolong long-term survival via the long-term memory function of the adaptive immune system [21,22]. Such response durability has been a hallmark of immunotherapy.

Pancreatic cancer immunotherapy can be classified as active or passive based on the involvement of the host immune system [5] and can be grouped into four categories according to the different immune response mechanisms activated by the cancer: specific active immunotherapy, specific passive immunotherapy, nonspecific adoptive immunotherapy and nonspecific immune regulation [4–6]. Specific active immunotherapy mainly comprises therapeutic cancer vaccines, which aim to activate the immune system to eventually result in the expansion of tumour-specific T/B cells [23]. Cancer vaccines can be generally divided into three major categories: cell-based vaccines, protein/peptide vaccines and genetic vaccines. Various genes or proteins have been targeted in recent I/II/III clinical trials of pancreatic cancer vaccines, such as telomerase and Wilms tumour gene [24,25]. Specific passive immunotherapy involves the direct infusion of tumour-specific immune effector cells or antibodies into a pancreatic cancer patient to mediate the immune response to the cancer. Monoclonal antibodies are currently the most widely adopted specific passive immunotherapy, including anti-endothelial growth factor receptor (EGFR) and anti-vascular epithelial growth factor (VEGF) antibodies, such as Erlotinib and Bevacizumab. A PD-1/PD-L1 blockade falls into this category of immunotherapy. A few studies have indicated that gemcitabine plus erlotinib shows favourable efficacy and safety and could significantly improve survival [26]. However, only a small subset of patients benefit. A phase II trial was designed to assess efficacy and safety of erlotinib with sorafenib in the treatment of advanced pancreatic cancer. Due to eight-week progression-free survival rate of 46% lower than the primary endpoint of a rate $\geq$70%, this study was suspended [27]. An international, open-label, phase III randomized trial, LAP07, enrolled 449 patients with locally advanced pancreatic cancer between 2008 and 2011. All patients received 4 months of induction chemotherapy to control the disease, and the results showed that there was no significant difference in overall survival between gemcitabine and gemcitabine plus erlotinib [28]. Nonspecific adoptive immunotherapy involves adoptively transferring processed highly specific immune cells or cytokines into patients to induce a passive immune response. In an early study, patients with advanced pancreatic cancer receiving adoptive immunotherapy using intraportal infusion of lymphokine-activated killer cells showed a lower rate of liver metastases and higher 3-year survival rate [29]. Another study indicated that adoptive immunotherapy with stimulated CTLs induced by co-culturing peripheral blood mononuclear cells and inactivated YPK-1 cells could significantly suppress the postoperative hepatic recurrence of pancreatic cancer [30]. Adoptive immunotherapy (cytokine-induced killer cells, CIKs) in patients with advanced gemcitabine-resistant pancreatic cancer was evaluated in a recent phase II trial conducted by Chung et al. The patients in this study showed an effective response to CIK therapy [31]. Nonspecific immune regulation involves therapy with immunomodulatory agents that do not directly kill a tumour but can strengthen the body's immunity and improve the patient's quality of life.

In recent decades, encouraging results regarding immunotherapy efficacy and its potential therapeutic application in pancreatic cancer have been obtained in various preclinical studies in murine models and in clinical trials. Although an immunosuppressive tumour microenvironment is prevalent in pancreatic cancer, recent developments in immunotherapies have provided many therapy strategies for the treatment of this deadly malignancy, such as in combination with other kinds of immunotherapy or chemoradiotherapy [32].

Development of targeting PD-1/PD-L1 in pancreatic cancer

Based on the previous introduction on PD-1/PD-L1, therapy targeting PD-1/PD-L1 in pancreatic cancer showed no apparent therapeutic effects. The majority of pancreatic cancers, with the exception of mismatch repair deficiencies, are regarded as immune-quiescent or resistant tumours and are non-responsive to single-checkpoint blockade therapies, such as anti-PD-1/PD-L1 and anti-CTLA-4 antibodies [32]. However, some advances still have been achieved in anti-PD-1/PD-L1 treatment of pancreatic cancer. A multicentre phase I trial in 2012 involved a total of 207 different types of cancer patients, including 14 pancreatic cancer patients, who were enrolled to validate the clinical evidence about the safety, clinical activity and pharmacokinetic and pharmacodynamic effects of anti-PD-L1 in advanced cancers. A total of 166 out of 207 patients responded to