Immunotherapy synergizes with chemotherapy targeting pancreatic cancer

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KEYWORDS: cancer stem cell • chemoimmunotherapy • pancreatic cancer

Pancreatic adenocarcinoma is a devastating disease and has an extremely poor prognosis. Despite aggressive treatment approaches, including surgery, chemotherapy and radiation, the overall 5-year survival rate is less than 5%. Therefore, the development of therapeutic strategies for advanced pancreatic cancer has traditionally been considered particularly challenging to improve clinical outcomes. Although immunotherapy that is designed to target tumor-associated antigens (TAAs) is a promising treatment approach, immunotherapy alone is limited by the number of cytotoxic T lymphocytes (CTLs) able to penetrate the large established pancreatic tumor. Even if large numbers of antigen-specific polyclonal CTLs were generated in vitro and injected into the patients, CTLs cannot penetrate into tumor sites because of stroma cells such as cancer-associated fibroblasts, tolerogenic dendritic cells (DCs), myeloid-derived suppressor cells (MDSCs), immunosuppressive tumor-associated macrophages and Tregs. Moreover, these cells produce immunosuppressive cytokines such as IL-10 and TGF-β; thus, clinical responses by immunotherapy alone cannot induce efficient antitumor immunity in patients with advanced pancreatic cancer. On the other hand, cytotoxic chemotherapy is well known to blunt immune responses, because of its toxicity for dividing cells including peripheral lymphoid tissue as well as the bone marrow. However, increasing evidence has been mounting to suggest that immunotherapy has the possibility of achieving better success when used in combination with chemotherapy [1]. For example, necrotic or apoptotic tumor cells induced by chemotherapy can be phagocytosed by DCs that are potent antigen-presenting cells, processed and presented to immune lymphocytes, followed by induction of antitumor immune responses. Different chemotherapeutic agents may kill tumor cells through an apparently homogeneous apoptotic pathway. Of note, treatment of pancreatic cancer cells with a standard cytotoxic agent for pancreatic cancer, gemcitabine, results in enhanced cross-presentation of TAAs by DCs and CTL induction [2]. Moreover, gemcitabine can also inhibit Tregs, B cells and MDSCs [2,3], but induce the proliferation of DCs [4]. These phenomena suggest that gemcitabine induces efficient CTL responses, improves the penetration of CTLs into the tumor parenchyma, and enhances tumor cell sensitivity to lyse antigen-specific CTLs. Thus, immunotherapy may mediate a potent antitumor effect when combined with chemotherapy.

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Now, the immunostimulatory effects of gemcitabine have been confirmed in clinical trials of patients with pancreatic cancer. Patients with advanced pancreatic cancer have been treated by combination therapy of gemcitabine with a single epitope peptide from VEGFR2 [5] or WT1 [6]. Both clinical and immune responses to the peptide vaccination combined with gemcitabine were observed and the immune responses were well correlated with overall survival. Recently, we reported that combination therapy of DC-based immunotherapies with chemotherapy such as gemcitabine and/or S-1 was effective in patients with advanced pancreatic cancer refractory to the chemotherapy [7]. In this regimen, DCs pulsed with peptides including WT1, tumor antigens
MUC1, CEA and/or CA-125 were combined with gemcitabine and/or S-1. Prior to the combination therapy, 46 out of 49 patients had been treated with chemotherapy, radiotherapy, heavy-particle radiotherapy or hyperthermia, but elicited no significant clinical effects. In spite of these handi capped conditions, of 49 patients, two patients showed complete response, five partial response and ten stable disease, and median survival time after the combination therapy was 360 days. Thus, chemoimmunotherapy may also especially benefit patients in whom salvage treatment was not effective. As WT1 and MUC1 are excellent TAA for the target of immunotherapy and are frequently expressed in pancreatic cancer cells [8], one promising treatment approach may be combination therapy of immunotherapy that targets TAA (WT1 and MUC1) and chemotherapy. Recently, we realized that some human pancreatic cancer cells showed upregulation of WT1 mRNA levels following treatment with chemotherapeutic agents including gemcitabine. Gemcitabine treatment also shifted WT1 protein from the nucleus to the cytoplasm, which promoted proteasomal processing of WT1 protein and presentation of WT1 peptide in MHC class I molecules on pancreatic cancer cells. Moreover, WT1-specific CTLs lized human pancreatic cancer cells treated with an optimal dose of gemcitabine more efficiently than untreated pancreatic cancer cells. Gemcitabine may enhance WT1 expression in human pancreatic cancer cells and sensitize human pancreatic cancer cells to the cytotoxic effect of WT1-specific CTLs [9]. Thus, WT1-specific CTLs induced by immunotherapy might kill pancreatic cancer cells already acquired gemcitabine resistance.

“A combined approach of conventional chemotherapy kills the bulk of cancer cells and immunotherapy that can keep residual CSCs and differentiated cancer cells in check may lead to an abrogation of the replenishing pool of pancreatic cancer cells.”

It has been well known that even if pancreatic cancer has apparently been defeated by chemotherapy, small populations of cells with cancer-initiating/cancer stem cell (CSC) fraction that can self-propagate and sustain tumor growth frequently lead to relapse and therapeutic failure [10]. Thus, CSCs are thought to be the culprit behind cancer metastasis and recurrence after clinical remission. The prognosis of patients with pancreatic cancer remains grim, and current thinking toward the development of curative therapy is likely to require eradication of CSC populations. Elimination of CSCs may lead to an abrogation of the replenishing pool of pancreatic cancer cells. Although CSCs are resistant to a variety of treatments, including chemotherapy and radiotherapy [11], CSCs are still a candidate target for immunotherapy. Indeed, after treatment with chemotherapy, CSCs showed increased levels of MUC1 expression and were efficiently killed by MUC1-specific CTLs [12]. Previously, CD44, CD24, ESA or CD133 had been used to identify a CSC population in pancreatic cancer [13]. On the other hand, both WT1 and MUC1 are shared antigens between CSCs and more differentiated subpopulations [8,14]; thus, the development of strategies that target the CSCs and differentiated cancer cells by WT1 and/or MUC1-specific CTLs may be highly desirable. In addition, immunotherapy using γδ T cells [15] or NK cells [16] can also kill human CSCs in vitro. However, success of the combination strategy depends on how well immunological responses against CSCs can be induced. DC-based cancer vaccines are one of the efficient strategies to initiate primary antitumor immune responses and overcome tolerance induction [17]. Indeed, hybrid cells generated by fusing DCs and CSCs endogenously processed multiple CSC-specific antigens including those yet unidentified, presented them in MHC class I and II pathways, and induced potent CSC-specific CTL responses in vitro [12]. Moreover, DCs pulsed with peptide from CSC-specific antigens or adoptive cell transfer of the CSC-specific CTLs generated in vitro may be another alternative approach for targeting chemotherapy-resistant CSC fraction. Moreover, the development of CSC-targeted immunotherapy has to overcome negatively regulated pathway by immunosuppressive cells. The success of immunotherapy with the anti-CTLA-4 antibody in metastatic melanoma [18] has interest in the development of immunotherapy for pancreatic cancer. Immunotherapies that struggle against pancreatic CSCs as well as more differentiated cancer cells with antigen-specific CTLs and depletion of immunosuppressive cells such as Tregs and MDSCs may tip the balance in favor of immunostimulation. A combined approach of conventional chemotherapy kills the bulk of cancer cells and immunotherapy that can keep residual CSCs and differentiated cancer cells in check may lead to an abrogation of the replenishing pool of pancreatic cancer cells; thus represent a more promising approach for the treatment of patients with advanced pancreatic cancer. Upcoming clinical trials will help us determine if this is indeed the case.
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