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Clinical impact of chemotherapy to improve tumor microenvironment of pancreatic cancer

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Abstract

A perioperative multimodal strategy including combination chemotherapy and radiotherapy, in addition to surgical resection, has been acknowledged to improve patient prognosis. However chemotherapy has not been actively applied as an immunomodulating modality because of concerns about various immunosuppressive effects. It has recently been shown that certain chemotherapeutic agents could modify tumor microenvironment and host immune responses through several underlying mechanisms such as immunogenic cell death, local T-cell infiltration and also the eradication of immune-suppressing regulatory cells such as regulatory T cells (Tregs) and myeloid-derived suppressor cells. With the better understanding of the cell components in the tumor microenvironment and the effect of chemotherapy to improve tumor microenvironment, it has been gradually clear that the chemotherapeutic agents is two-edged sword to have both immune promoting and suppressing effects. The cellular components of the tumor microenvironment include infiltrating T lymphocytes, dendritic cells, regulatory T cells, tumor associated macrophages, myeloid derived suppressor cells and cancer associated fibroblasts. Based on the better understanding of tumor microenvironment following chemotherapy, the treatment protocol could be modified as personalized medicine and the prognosis of pancreas cancer would be more improved utilizing multimodal chemotherapy. Here we review the recent advances of chemotherapy to improve tumor microenvironment of pancreatic cancer, introducing the unique feature of tumor microenvironment of pancreatic cancer, interaction between anti-cancer reagents and these constituting cells and future prospects.

Key words: Pancreas cancer; Microenvironment; Chemotherapy; Immune cells; Immunomodulation

Core tip: It has been gradually clear that the chemotherapeutic agents are two-edged sword to have both immune promoting and suppressing effects. The cellular

components of the tumor microenvironment including infiltrating T lymphocytes, dendritic cells, regulatory T cells, tumor associated macrophages, myeloid derived suppressor cells and cancer associated fibroblasts could be improved. Based on the better understanding of tumor microenvironment following chemotherapy, the treatment protocol could be modified as personalized medicine and the prognosis of pancreas cancer would be more improved utilizing multimodal treatment strategy.

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INTRODUCTION

Pancreatic carcinoma is an extremely aggressive malignant tumor and the fifth leading cause of death worldwide and is expected to be the second by 2030 in Western countries[1,2]. The only curative option is surgical resection, but the 5-year overall survival (OS) rate still needs to be improved from the current 10%-15% even after curative resection[1,3]. A perioperative multimodal strategy including combination chemotherapy and radiotherapy, in addition to surgical resection, has been acknowledged to improve patient prognosis. New cytotoxic agents such as gemcitabine, Tegafur-gimeracil-oteracil potassium (TS-1) and combination chemotherapy with 5-fluorouracil (5-FU), oxaliplatin, and irinotecan along with perioperative chemoradiotherapy before and after surgery have recently been widely investigated[4,5]. Chemotherapy, usually a standard treatment option for cancer, has not been actively applied as an immune-modulating modality because of concerns about various immunosuppressive effects. However, certain chemotherapeutic agents have recently been shown to improve host immune responses and even break immune tolerance[6]. Several underlying mechanisms have been clarified, including immunogenic cell death[7,8], local T-cell infiltration and also the eradication of immune-suppressing regulatory cells such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), all of which are associated with cells in the tumor microenvironment[9]. On the other hand, care must be taken that chemotherapy-induced cancer metastasis does occur during treatment through non-immunological pathways[10].

We review recent advances in chemotherapeutic regimens to improve the tumor microenvironment for pancreatic cancer, and introduce unique features of the tumor microenvironment for pancreatic cancer, interactions between anti-cancer reagents and the constituent cells, and future prospects.

OVERVIEW OF STANDARD CHEMOTHERAPY AND CHEMORADIATION THERAPY FOR PANCREATIC CANCER

Although the only curative option is surgical resection, with the advances in perioperative strategy for pancreatic carcinoma, many cytotoxic agents have proven effective in treating this disease. Chemoradiation therapy had been also adopted aiming at locoregional response and additional effects outside the field of irradiation (abscopal effects)[11].

Representative cytotoxic agents include historical 5-FU monotherapy, gemcitabine monotherapy, and gemcitabine-based combination therapies[4]. The following randomized controlled trials are investigations recently undertaken try to improve the chemotherapeutic strategy for pancreatic cancer. Burris *et al*[12] had shown for the first time that gemcitabine was superior to 5-FU in terms of overall survival, thus suggesting gemcitabine as a key drug in advanced pancreatic cancer. In 2011, FOLFILINOX (5-FU, leucovorin, irinotecan and oxaliplatin) had been shown to have survival benefit over gemcitabine alone in patients with metastatic pancreas cancer[13]. Recently Nab-paclitaxel plus gemcitabine have been reported to have superior efficacy compared with gemcitabine monotherapy in metastatic pancreas cancer (MPACT trial)[14]. However, MPACT trial, consisting of Gem + Nab-paclitaxel had OS of 8.5 mo compared to 6.7 mo in patients treated with gemcitabine alone) suggesting minimal improvement of survival by current chemotherapy regimens and requiring for further developments.

Taken together, overall survival of patients with metastatic disease extended to nearly 1 year from around 6 mo in the preceding two decades, thanks to recent therapeutic advances. However, although these reagents are promising, median progression-free survival remains limited and the 5-year survival rate of patients is still unsatisfactory, at around 15%-20%, even with these multimodal treatment strategies. This is due in part to dose limiting toxicity of side effects such as neuropathy and bone marrow suppression and due also to chemoresistance, relapse and metastasis even after surgical resection.

TUMOR MICROENVIRONMENT OF PANCREATIC CANCER

Tumor cells alone were initially considered the specific target of chemotherapy, leading to a focus on the cytotoxicity of agents inhibiting DNA repair, tubulin formation and cell proliferation[15]. However, recent research has identified the tumor microenvironment as comprising tumor cells, host immune cells such as T cells, Tregs and MDSCs, and cancer-associated fibroblasts or stromal cells that support or suppress each

Table 1 Targets of chemotherapy to improve tumor microenvironment

Cellular components	Target molecules	Chemotherapeutic agents	Underlying mechanism	Ref.
TIL	CD4, CD8 positive T lymphocytes	GEM, TS-1,	Increase lymphocyte infiltration	[22]
	RAS/MAPK	MEK inhibitor, PD1/PDL1 immune checkpoint inhibitors		[24]
DC		GEM	Proliferation of DC and CTL	[26]
Treg	CD4 and FoxP3 positive T lymphocytes	GEM, cyclophosphamide	Depletion	[21]
MDSC	CCL2, CCR2, GMCSF	GEM, 5-FU	Increase differentiation	[34,35]
			Depletion	[5]
CAF	Palladin positive fibroblasts	GEM	Depletion	[38]
	mTOR/4E-BP1 pathway	GEM, Pasireotide	Reduce tumor growth and chemoresistance	[39]

TIL: Tumor infiltrating lymphocytes; DC: Dendritic cells; Treg: Regulatory T cells; TAM: Tumor associating macrophages; MDSC: Myeloid derived suppressor cells; CAF: Cancer associated fibroblasts; Gem: Gemcitabine; 5-FU: 5-fluorouracil.

other[9]. Each of these cellular components contributes to treatment response and patient prognosis, with tumor cells forming a network through direct interactions and cytokines providing important signals to initiate cell invasion into vessels and lymph nodes, leading to distant metastasis. Desmosomes are also one of the specific features of pancreas carcinoma that make drug delivery so difficult and prevent immune cells from infiltrating to tumor nests[16].

These evidences collectively indicate that tumor cells are thought to grow, interacting with the microenvironment, highlighting the need to clarify the specific mechanisms by which each chemotherapeutic agent improves the tumor microenvironment to contribute to treatment efficacy.

The following sections are arranged to describe recent evidence for the effects of chemotherapeutic agents on the cellular components of the tumor microenvironment (Table 1).

INFILTRATING T LYMPHOCYTES

A number of reports have suggested that the accumulation of CD4 and CD8 lymphocytes in solid tumors offers a good prognostic indicator for patient survival[17,18]. In terms of pancreatic cancer, Tewari *et al*[19] demonstrated a positive correlation between prognosis and the presence of tumor infiltrating T cells. Although the clinical relevance differs among types of cancer, in association with the HLA class I expression level[20], some agents have been reported to induce T-cell infiltration into pancreas cancers[21]. Homma *et al*[22] showed that $CD4^+$ and $CD8^+$ cells were significantly increased after neoadjuvant chemotherapy comprising gemcitabine and TS-1 followed by radiotherapy (NACRT), and a high accumulation of $CD4^+$ cells offered a good prognostic marker for pancreas carcinoma after NACRT. Teng *et al*[23] recently classified the types of tumor microenvironment based on the presence or absence of T-cell infiltration and expression of PD1 along with patient prognosis.

Loi *et al*[24] recently suggested that therapeutic cooperation of MEK and PD-1/PD-L1 immune check point inhibitors could increase tumor-infiltrating lymphocytes through RAS/MAPK pathways in breast cancer. Great expectations are held for increased control of the tumor microenvironment, especially with tumor-infiltrating lymphocytes enabling further improvements in patient prognosis associated with immune check point inhibitors.

DENDRITIC CELLS

Dendritic cells are the most potent antigen presenting cells and play a crucial part in the initiation, programing, and regulation of antitumor immunity, directing cytotoxic T lymphocytes and natural killer cells to become potent antitumor effectors capable of eradicating malignant cells[25,26]. Recently it had been reported that dendritic cells are impaired in number and display maturation defects disable to function as antigen presenting cells in pancreatic cancer due to the inflammation of the disease[27]. Meanwhile, chemotherapy can promote immunogenic cell apoptosis enhancing immunogenicity and mediating efficient phagocytosis by dendritic cell[7]. Moreover, gemcitabine can enhance the cross presentation of tumor associated antigens by dendritic cells and as well as inducing the proliferation of DC and CTL[26]. Those strategies utilizing chemotherapeutic agents might be useful to overcome negative microenvironment.

REGULATORY T CELLS

Tregs are defined as T cells expressing both CD4 and forkhead box P3 (FoxP3), and are usually associated with poor prognosis and immunosuppression in various cancers. Transcriptional FoxP3 is a crucial intracellular marker and also a key developmental and functional factor for $CD4^+FoxP3^+$ Tregs[28]. In terms of pancreatic cancer, multimodal chemotherapy including GEM, cyclophosphamide, and taxane has been demonstrated to decrease Tregs in the tumor microenvironment[5]. Low Treg percentage in circulation at 1 year after PC resection had been correlated with improved survival[29]. We have also previously shown that neoadjuvant treatment of pancreatic ductal adenocarcinoma with chemotherapy and chemoradiotherapy can alter the

local Treg balance in favor of antitumor immunity in resected human sections[21]. Another paper by Keenan *et al*[30] showed that immunization of mice with Listeria Monocytegenes engineered to express k-ras along with depletion of Treg cells reduced progression of early stages PanINs. Also, Shibuya *et al*[31] recently reported that CD8 effector T cells show marked accumulation in the tumor microenvironment, but are suppressed by Tregs and PD-L1 expressed on T cells. These findings have therefore led to expectations for novel strategies of multimodal chemotherapy in combination with immune checkpoint inhibitors reducing Tregs.

TUMOR-ASSOCIATED MACROPHAGES

Tumor-associated macrophages (TAMs) are derived from $CCR2^+$ monocytes in the spleen and peripheral blood, infiltrating into the tumor and developing into macrophages on stimulation by the releasing hormone CCL2 and colony-stimulating factor 1 (CSF-1)[32,33]. TAMs have recently been reported to limit the effects of chemotherapy and promote tumor chemoresistance[34]. Michem et al. reported that targeting TAMs by inhibiting CSF1R or C-C chemokine receptor 2 (CCR2) could decrease the number of pancreatic tumor-initiating cells and improve chemotherapeutic efficacy *in vivo*. The Denargo group reported that the combination of cytotoxic chemotherapy and blockade of CSF1R, which is prominently expressed by monocytes, Mo-MDSC and macrophages, resulted in improved anti-tumor T-cell responses[32]. Furthermore, Sanford *et al*[33] reported that the CCL2/CCR2 chemokine axis plays a crucial role in the recruitment of inflammatory monocytes from bone marrow to peripheral sites of inflammation and an increased ratio of inflammatory monocytes in blood compared to bone marrow offers a novel predictor of decreased patient survival following tumor resection. These lines of evidence clearly show that chemotherapy combined with chemokine blockade might reduce the chemoresistance associated with the exclusion of TAMs.

MYELOID DERIVE SUPPRESSOR CELLS

MDSCs are heterogeneous populations of immune cells derived from progenitor cells in bone marrow. MDSCs with a phenotype of $CD33^+HLA\text{-}DR^{-/low}$ that are lineage-negative ($CD14^-$, $CD15^-$) are well described as immunosuppressive in cancer patients contributing to tumor progression by damping T-cell immunity and promoting angiogenesis[35,36]. Many chemotherapeutic drugs have long been thought to exclude MDSCs from various cancers. Zheng *et al*[5] showed that GEM and 5-FU have a direct killing effect on MDSCs. In contrast, Takeuchi *et al*[36] reported that GEM could increase MDSC numbers through increases in GM-CSF levels, converting M2 macrophages into suppressive MDSCs. Therefore MDSC in peripheral blood might be a possible predictive biomarker of chemotherapy failure in PC patients[37]. Also, GEM and 5-FU have been reported to activate NLRP3 inflammasomes in MDSCs, leading to interleukin-1β release, which restrains their antitumor efficacy[38]. More recently, Hu *et al*[39] reported TNFB2R as important for its suppressive function. Uniquely, Sanford *et al*[40] recently reported the clinical utility of zoledronic acid. This agent is usually utilized to improve calcium imbalances in patients osteoporosis, but also prevents tumor-mediated myelopoiesis associated with the generation of MDSC. Further studies are warranted to adjust the balance between direct reduction of MDSCs and indirect promotion of MDSCs by chemotherapy in combination with the multimodal strategies described above.

CANCER-ASSOCIATED FIBROBLASTS

Fibrous stroma associated with cancer in the tumor micro environment has increasingly been recognized as involving cancer-associated fibroblasts (CAFs). These cells are reported to contribute to poorer survival in various tumors, including pancreatic ductal adenocarcinoma, which has been reported to contain large numbers of CAFs[41]. The characteristically dense desmosome in pancreatic cancer acts as a barrier to drug delivery, thus contributing to chemoresistance[4]. Among the many markers of CAFs, Sato *et al*[41] reported that palladin, a CAF marker, could represent an independent marker of poor prognosis and a biomarker to predict the efficiency of chemotherapy or even disease recurrence. Duluc *et al*[42] recently revealed one of the underlying mechanisms abrogating pancreatic cancer chemoresistance through the mTOR/4E-BP1 pathway, allowing GEM-based chemotherapy combined with sst1 receptor-activating pasireotide to reduce tumor growth and chemoresistance. This kind of anti-stromal targeted therapy could be expected in addition to host immune cell-targeted therapy, as an adjunct to direct killing of cancer cells.

DISCUSSION

With our developing understanding of the cell components in the tumor microenvironment and the effects of chemotherapy in improving this environment, chemotherapeutic agents have gradually been revealed to represent a two-edged sword with effects that both promote and suppress immunity[5]. Such therapies deplete one factor of immune suppression while at the same time inducing another mechanism to inhibit host immune responses. Some experimental data in this paper show that these problems might be overcome by multimodal combination chemoimmunotherapy in addition to standard chemotherapy, blocking antibodies for cytokine release or utilizing immune checkpoint inhibitors. Beaty *et al*[43] reported combining chemotherapy with the agonist CD40, as a member of the TNF receptor superfamily, for surgically incurable PDA and observed tumor regression in some patients. Takeuchi *et al*[36] likewise reported that anti-GM-CSF

antibody blocking could accelerate the formation of immunosuppressive myeloid cells in the tissue microenvironment of human pancreatic cancer.

Chemotherapeutic protocols including timing and dose might also be further explored and modified based on both reductions in tumor size and the induction of anti-tumor-specific immunity. Metronomic chemotherapy or low-dose chemotherapy has been reported to induce anti-tumor T-cell immunity *in vivo*[44]. One of the underlying mechanisms might be that such low-toxicity doses of cytotoxic agents induce minimal suppression of tumor cells while concomitantly inducing minimal suppression of immune-promoting cells based on altered immune balance.

Lastly, future evidence should be accumulated regarding these balances in the tumor microenvironment during multimodal chemotherapy by measuring biomarkers locally and systematically. Biopsy specimens provide information of infiltrating T lymphocyte levels in the tumor microenvironment, offering possible predictors of beneficial response to chemotherapy in breast and pancreas cancers. SPARC expression levels in the stroma could represent a target for nab-paclitaxel. Although data must continue to be accumulated, miRNA might reflect changes in immune balances and predict the efficacy of chemoimmunotherapy[45]. Taking all these lines of evidences together in combination with the properties of emerging agents, current problems seem likely to be overcome, at least in part, and the prognosis of pancreas cancer can be expected to continue improving in the coming decades.

CONCLUSION

The chemotherapeutic agents have both immune promoting and suppressing effects in the tumor microenvironment of pancreatic cancer. Based on the better understanding of tumor microenvironment following chemotherapy, the treatment protocol could be modified as personalized medicine and the prognosis of pancreas cancer would be more improved utilizing multimodal chemotherapy.

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