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MINIREVIEW

Current developments, problems and solutions in the non-surgical treatment of pancreatic cancer

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Abstract

Pancreatic cancer is a common malignant neoplasm of the pancreas with an increasing incidence, a low early diagnostic rate and a fairly poor prognosis. To date, the only curative therapy for pancreatic cancer is surgical resection, but only about 20% patients have this option at the time of diagnosis and the mean 5-year survival rate after resection is only 10%-25%. Therefore, developing new treatments to improve the survival rate has practical significance for patients with this disease. This review deals with a current unmet need in medical oncology: the improvement of the treatment outcome of patients with pancreatic cancer. We summarize and discuss the latest systemic chemotherapy treatments (including adjuvant, neoadjuvant and targeted agents), radiotherapy, interventional therapy and immunotherapy. Besides discussing the current developments, we outline some of the main problems, solutions and prospects in this field.

Key words: Treatment; Pancreatic cancer; Survival rate; Systemic chemotherapy; Radiotherapy; Interventional therapy; Immunotherapy

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INTRODUCTION

Pancreatic cancer is a malignant neoplasm of the pancreas whose prognosis is fairly poor. The incidence rate has risen in recent years and it comprises 1%-2% of common tumors. Each year about 185 000 individuals globally are diagnosed with this condition. As its symptoms are usually non-specific, pancreatic cancer is often not diagnosed until and advanced stage. The only potentially curative therapy for pancreatic cancer is surgical resection. Unfortunately, only 20% patients are resectable at the time of diagnosis. Even among those patients who undergo resection for pancreatic cancer and have tumor-free margins, the 5-year survival rate is only 10%-25%[1]. Therefore, developing new treatments to improve the survival rate has practical significance for patients with pancreatic cancer.

SYSTEMIC CHEMOTHERAPY

Recent developments

The purpose of systemic chemotherapy is to relieve symptoms, improve the quality of life and prolong survival.

Chemotherapy

Compared with no chemotherapy or best supportive care, the combination of 5-fluorouracil (5-FU) with other drugs shows survival benefit in patients with pancreatic cancer. However, a retrospective study involving 5365

patients with pancreatic cancer showed no difference in survival between 5-FU combination therapy and 5-FU monotherapy[2].

Gemcitabine (GEM) is a metabolic anti-tumor drug and has been approved by the United States Food and Drug Administration as the standard treatment for pancreatic cancer. The use of gemcitabine-cisplatin (GC) or capecitabine shows superiority over GEM monotherapy, while studies comparing GEM plus irinotecan or fluorouracil with GEM monotherapy show conflicting results. In studies of GC therapy, partial response (PR) was 10%-30%, time to tumor progression (TTP) was 2.8-7 mo, and median survival time (MST) was 5.6-8.1 mo[3]. In studies of GEM in combination with capecitabine therapy, PR was 8.9%, stable disease (SD) was 42%, TTP was 6.5 mo, overall survival (OS) was 8 mo, one-year survival rate was 34.8%, 53% of the patients experienced less pain, 44% of the patients reduced the dosage of analgesic, and 36% of the patients gained weight[4].

Capecitabine is an orally-administered prodrug that is enzymatically converted to 5-FU. When used as first-line drug in patients with pancreatic cancer, its response rate (RR) is 24%. Therefore, it is recommended as the second-line drug for pancreatic cancer patients who failed GEM. Capecitabine monotherapy as second-line treatment for pancreatic cancer has only been studied in phase Ⅱ trials, which showed that RR was 37%, TTP was 2.2 mo, and MST was 7.5 mo[5]. In studies of capecitabine plus oxaliplatin plus capecitabine as second-line treatment for advanced pancreatic cancer, RR was 28.2%, TTP was 9.9 wk, MST was 23 wk. The main side effect was fatigue and there were no severe hematological or nervous system side effects[6]. Capecitabine in combination with docetaxel showed a RR of 50%-83%, but showed no survival benefit because of frequent side effects such as grade 3-4 neutropenia, gastrointestinal reaction, and hand-foot syndrome[7]. Phase Ⅱ clinical trials of capecitabine in combination with celecoxib as second-line treatment for pancreatic and bile duct cancer showed RR was 30% and MST was 16 wk[8].

The addition of cetuximab to adjuvant gemcitabine was investigated in an open label, multi-center, phase Ⅱ trial reported by Fensterer *et al*[9]. Patients underwent R0 or R1 resection for pancreatic cancer, and were then treated with adjuvant chemotherapy consisting of 6 cycles of gemcitabine with weekly cetuximab for 24 wk. Of 76 patients enrolled, 73 patients received at least one dose of cetuximab. Median disease free survival (DFS) was 11.9 mo, and the DFS rate at 18 mo was 33.5%, failing to exceed the 35% level hypothesized by the authors. Median OS was 21.5 mo (95%CI: 16.9-28.2). Grade 3 or 4 toxicities were neutropenia in 11% of patients, thrombocytopenia in 8.2%, dermatological reaction in 6.9%, and allergic reaction in 6.9%. The authors concluded that the addition of cetuximab to gemcitabine in the adjuvant treatment of pancreatic cancer does not improve DFS compared with the use of gemcitabine alone.

S-1 and tegafur are also orally-administered 5-FU prodrugs. Studies of tegafur as first-line monotherapy or combination therapy for advanced pancreatic cancer are ongoing. S-1 is a new orally-administered chemotherapy drug that combines tegafur with 5-chloro-2,4-dihydroxypyridine and oteracil at the ratio 1:0.4:1. Currently, its main use is in treating progressive stomach cancer. GEM in combination with S-1 was well tolerated and highly effective in patients with advanced pancreatic cancer in a phase Ⅰ study. PR was 44%, SD was 48%, OS was 10.1 mo, and one-year survival rate was 33%. The side effects were acceptable and neutropenia was the most common, with an incidence rate of 80%[10].

Currently, the use of camptothecins is limited in patients with pancreatic cancer. In studies of irinotecan monotherapy as second-line treatment for pancreatic cancer, RR was 48%, MST was 6.6 mo. Severe nausea occurred in 64% of the patients, and diarrhea occurred in 36%[11]. When used as second-line drug, camptothecins showed no survival benefit and demonstrated severe side effects. Rubitecan, an orally-administered camptothecin analog, failed to show positive effects. In a open-label phase Ⅱ trial, RR of rubitecan monotherapy was only 7%, and MST was 3 mo[12]. In studies of paclitaxel monotherapy, RR was 6% and MST was 17.5 wk. It was well tolerated, with mild gastrointestinal reaction and hematological side effects.

In studies of pemetrexed monotherapy and raltitrexed monotherapy as second-line treatment for patients who failed GEM, RR was very low (0%-3.8%), MST was 18-20 wk. When used in combination with oxaliplatin or irinotecan, MST was 21-26 wk and showed more grade Ⅲ-Ⅳ side effects[13].

Adjuvant and neoadjuvant therapy

Early stage pancreatic cancer is generally asymptomatic. As a result, the disease is often locally advanced or metastatic at the time of diagnosis, meaning that surgical treatment can only be performed in a minority of the cases. Furthermore, recurrence may occur after resection. Therefore, adjuvant chemotherapy and radiotherapy are very important for the treatment of this disease. 5-FU or GEM in combination with radiotherapy are widely used and have been showed to significantly increase the quality of life and prolong survival[14]. Adjuvant chemotherapy has shown a trend towards improved OS. Comparison of use of gemcitabine *vs* 5-FU was explored in the ESPAC-3 trial, which demonstrated equivalent survival for both treatments, but a more favorable safety profile with gemcitabine. There was also a trend toward improved survival in the gemcitabine arm in patients with node positive disease or those with positive resection margins[15].

Kwon *et al*[16] conducted a phase Ⅱ trial of adjuvant gemcitabine and cisplatin chemotherapy followed by chemoradiation with gemcitabine and 5040 cGy of radiation, then 4 cycles of maintenance gemcitabine. Of the patients enrolled, 57 completed chemotherapy followed by chemoradiation. One-year DFS rate was 62.1%, median DFS was 17.4 mo, and median OS was 33.6 mo.

The majority of recurrences (66.2%) were distant metastases. Later disease stage and involved lymph nodes were associated with reduced DFS ($P < 0.001$ and $P = 0.01$, respectively). These finding suggest promising efficacy with acceptable toxicity for adjuvant multimodality therapy.

The aim of neoadjuvant therapy is to turn the tumor from unresectable to resectable by reducing the volume. However, studies of neoadjuvant therapy in patients with pancreatic cancer at different stages showed conflicting results.

Neoadjuvant 5-FU-based chemotherapy showed modest effects for resectable tumors. 5-FU plus platinum anticancer drugs showed significantly improved effects. Trials of GEM as neoadjuvant therapy showed improvement in MST. However, a recently published retrospective analysis showed conflicting conclusions. Some studies indicated that neoadjuvant therapy for resectable tumor helped to improve CR, reduce the recurrence rate, and improve survival rate, while others suggested that neoadjuvant therapy showed no survival benefit and increased postoperative complications. Neoadjuvant therapy for resectable pancreatic tumor is still at the experimental stage and is not recommended as standard treatment.

The current neoadjuvant therapy for advanced local tumors is concurrent chemoradiotherapy. Studies of this therapy have demonstrated significant variation in its curative effects. This may be owing to the difference in the definition of "unresectable". Moreover, such retrospective studies may have sample selection bias[17].

Molecular targeted therapies

These therapies are based on molecular biological differences between tumor and normal cells. They can inhibit the proliferation of tumor cells and promote their apoptosis by blocking signal transduction and prevent tumor angiogenesis. They interfere with specific targeted molecules needed for carcinogenesis and tumor growth, so they are more effective than conventional chemotherapy and less harmful to normal cells.

Epidermal growth factor receptor-targeted drugs: Epidermal growth factor (EGF) and epidermal growth factor receptor (EGFR) are overexpressed in the cells of pancreatic tumors, and are indicators of high aggressiveness and poor prognosis. Therefore, EGFR-targeted therapy is a promising strategy for the treatment of pancreatic tumor.

Cetuximab (C-225) is a chimeric monoclonal antibody, which is an inhibitor of EGFR. It prevents the growth of tumor cells by binding to the extracellular domain of EGFR, inhibiting phosphorylation caused by receptor-ligand binding, and blocking the EGFR-mediated signaling pathway. At the same time, it inhibits tumor angiogenesis and metastasis by reducing essential factors such as vascular endothelial growth factor (VEGF). Cetuximab in combination with GEM showed additive effects in patients with advanced pancreatic cancer[18]. Phase I trials showed that cetuximab was well tolerated when used either as monotherapy or in combination with other cytotoxic drugs or chemotherapy. Cetuximab in combination with 5-FU, GEM, carboplatin or cisplatin demonstrated no drug interaction[19]. Phase Ⅱ trials indicated that cetuximab in combination with GEM was effective in advanced pancreatic cancer although further clinical trials are needed.

Erlotinib, an EGFR tyrosine kinase inhibitor, is a small molecule compound that targets EGFR tyrosine kinase by blocking autophosphorylation and the downstream signal transduction pathway. According to results published at the 2005 American Society of Clinical Oncology annual meeting, GEM in combination with erlotinib showed longer one-year survival than GEM monotherapy. Therefore, GEM in combination with erlotinib is the only Food and Drug Administration approved combination therapy for unresectable or metastatic pancreatic cancer[20]. Moreover, a study of erlotinib plus capecitabine in 30 patients who failed GEM-based therapy showed that the combination therapy was well tolerated and that the outcome was positive[21]. No significant positive effects were observed in clinical trials of gefitinib.

ErbB-2 is a member of the receptor tyrosine kinase family and is over-expressed in cells of pancreatic tumors. Herceptin is a monoclonal antibody that suppresses proliferation of tumor cells with ErbB-2 overexpression. A study of GEM plus Herceptin showed RR was 6%, MST was 7 mo, and one-year survival rate was 19%, which was similar to results from GEM monotherapy.

VEGF receptor inhibitors: VEGF stimulates endothelial cell proliferation and angiogenesis, inhibits endothelial cells apoptosis by activating HSP90 and Bcl-2 expression, increases intercellular gaps and vascular permeability by making endothelial cells produce nitric oxide. It thus promotes tumor migration, activates kinase activity by autophosphorylation, triggers signal transduction, and stimulates tumor angiogenesis.

Bevacizumab is a humanized monoclonal antibody that recognizes and blocks VEGF-A. It blocks the chemical signal that stimulates the growth of new blood vessels and inhibits tumor angiogenesis and tumor cell proliferation. A study of bevacizumab in combination with GEM showed PR was 21% (11 patients), SD was 46% (24 patients), six-month survival rate was 77%, MST was 8.8 mo, and side effects included increased blood pressure (19%), thrombosis (13%), perforation of abdominal viscera (8%) and hemorrhage (2%)[22]. A multicenter phase Ⅱ trial of GEM in combination with bevacizumab in pancreatic cancer demonstrated encouraging results, giving rise to optimism for further research on bevacizumab in combination with chemotherapy.

AEE788 is a new molecular-targeted drug and kinase inhibitor with potent inhibitory activity against ErbB and the VEGF receptor family of tyrosine kinases. It inhibits EGFR overexpression and VEGF-mediated growth of vascular endothelial cells. In animal experiments, AEE788 in combination with GEM showed higher control rate

(95%), increased cell apoptosis, reduced angiogenesis, and extended survival in mice with transplanted pancreatic tumors. Relevant phase I trials are underway[23].

Matrix metalloproteinases inhibitors: Matrix metalloproteinases (MMPs) promote tumor cell invasion and migration, and stimulate tumor angiogenesis by degrading extracellular matrix and basement membrane, thereby regulating cell adhesion. Marimastat is an orally-administered broad-spectrum MMP inhibitor. It was well tolerated and showed a similar survival rate (19%-20%) to GEM monotherapy in patients with advanced pancreatic cancer[24]. There was no that its therapeutic effect may improve when used in combination with other drugs.

Prostaglandin synthase: Cyclooxygenase-2 (COX-2) plays an important role in the development and progression of tumors. It activates epithelial cell proliferation, inhibits tumor cell apoptosis, stimulates tumor angiogenesis, improves tumor cell invasion, and induces immunosuppression and mutation, in which angiogenesis is closely associated with malignant tumor growth, invasion and migration. Celecoxib is a highly selective COX-2 inhibitor. In a clinical trial involving 42 patients with advanced pancreatic cancer, celecoxib in combination with GEM showed CBR of 54.7%, MST of 9.1 mo, and only mild side effects[25]. However, no improved therapeutic effect or survival benefit (MST was 5.8 mo) was observed in studies of celecoxib plus GEM and DDP.

Farnesyl protein transferase inhibitors: Farnesyl protein transferase (FPT) is a critical enzyme for Ras protein synthesis. Therefore, inhibiting FPT and the activity of *Ras* gene may be a means to treat pancreatic cancer. FPT inhibitors include lonafarnib (SCH66336) and tipifarnib, BMS-214662. However, phase I and phase II trials of tipifarnib monotherapy in patients with advanced pancreatic cancer showed disappointing results[26].

Problems

The anatomical structure of the pancreas is very complicated. The high interstitial tension and inadequate blood perfusion of solid tumors, especially pancreatic tumors, give them extreme resistance to most chemotherapy drugs. Consequently, conventional systemic intravenous chemotherapy often fail to reach effective concentration[27]. Large dosages may cause severe adverse reactions, thus impairing the immune system and therapeutic effect.

GEM has replaced 5-FU as the most widely used drug in advanced pancreatic cancer. GEM and GEM-based combination therapies are recommended as standard for advanced pancreatic cancer by National Comprehensive Cancer Network. Several combination therapies based on GEM and 5-FU have been developed, although their therapeutic effects are still unknown. So far, they have mainly demonstrated improvement in the control of tumor growth and it remains unclear whether or not they have survival benefits.

No randomized controlled prospective study of neoadjuvant therapy for pancreatic cancer has been conducted and, therefore, can not be recommended as treatment for pancreatic cancer, other than in clinical trials.

As the molecular pathway of tumor cellular differentiation, migration, apoptosis and metabolism are not clear, targeted cancer therapies still lack specificity.

Solutions and prospects

In order to minimize the side effects of combination therapy, more data from phase II trails of monotherapy and combination therapy should be collected.

More clinical trials of topical medication, such as regional perfusion chemotherapy should be conducted. The arterial blood supply of the pancreas is from the common hepatic artery (division of the celiac artery), splenic artery, and superior mesenteric artery. Anti-tumor drugs infused through celiac artery or superior mesenteric artery can reach the whole pancreas. Hepatic artery infusion is also effective in pancreatic cancer metastices in the liver. The commonly used drugs include 5-FU, cisplatin, epirubicin, mitomycin and GEM. Regional perfusion significantly increases drug concentration within the pancreas, prolongs the presence of the drug in the body, and causes fewer side effects on other important organs, indicating its effectiveness in pancreatic cancer. Infusion *via* cannula of embolic agents into arteries that supply blood to the pancreas prolongs the presence of the drug in the body, reduces blood supply to the tumor, increases the cytotoxicity of the drug, and leads to necrosis of tumor cells. Studies showed that local ischemia inhibited the synthesis of DNA and protein of tumor cells, thereby inhibiting the growth of transplanted pancreatic tumors in mice.

Intra-tumor injection of chemotherapy drugs can break the blood-pancreatic barrier, increase drug concentration within the tumor, and causes fewer sides effects than systemic chemotherapy. This is a good option for patients with unresectable pancreatic tumors.

We need to identify the molecular pathway of pancreatic cancer and look for highly specific targets. For example, S100P may reduce the side effects of chemotherapy drugs, breast cancer type 2 susceptibility protein may enhance pancreatic cancer's sensitivity to mitomycin, and human equilibrative transporter 1 overexpression can improve the survival rate of patients received GEM therapy[28]. This may be helpful to the future treatment for pancreatic cancer.

Pancreatic cancer cells are resistant to conventional treatments because they carry mutations which inhibit the activation of apoptosis. Therefore, developing a molecular targeted drug that inhibits mutation may be a solution.

RADIOTHERAPY

Recent developments

In recent years, the development of radiotherapy techniques, knowledge about the localization of tumor and radiation dosage have provided new and effective treat-

ment for pancreatic cancer.

X knife: This is a linear accelerator delivering high-energy X-rays to the region of the patient's tumor. Only a few cases of pancreatic cancer treated with the X knife have been reported. The X knife is only good option for pancreatic cancer treatment in patients diagnosed with early stage of the disease[29].

Three-dimensional conformal radiotherapy: The profile of each radiation beam is shaped to fit the profile of the target from a beam's eye view, using lead or a multileaf collimator and a variable number of beams. When the treatment volume conforms to the shape of the tumor, the relative toxicity of radiation to the surrounding normal tissues is reduced, allowing a higher dose of radiation to be delivered to the tumor than when using conventional techniques. This is the most widely used radiotherapy technique for pancreatic cancer[30]. Studies showed that it relieved jaundice in patients with carcinoma of the pancreatic head, and one-year and two-year survival rates were 60%-90% and 25%-70%, respectively. A recent study showed one-year and two-year survival rates of 55.6% and 27.8% respectively, significantly higher than the 33% and 9.4% of traditional radiotherapy. Therefore, 3-dimensional conformal radiotherapy for local advanced pancreatic cancer will be the focus of future research.

Intensity modulated radiation therapy: This technique allows high radiation doses to be focused on regions within the tumor while minimizing the dose to surrounding normal critical structures, especially the dose to the duodenum. Therefore, higher and more effective radiation doses can safely be delivered to tumors with fewer side effects compared with conventional radiotherapy techniques[31]. This may make it be a suitable radical treatment for early stage local pancreatic cancer. Further clinical researches on this therapy are of great significance.

Precision radiation therapy: This method delivers a single high-dose of precisely-targeted radiation using highly focused gamma-ray beams that converge on the specific area where the tumor or other abnormality resides. In advanced pancreatic cancer patients who are not suitable for surgery, stereotactic radiotherapy may help control the growth of tumor, reduce jaundice, relieve symptoms, improve appetite, and improve the quality of life. "Gamma knife" is abbreviation of "gamma knife stereotactic radiosurgery system", and is composed of a radioactive source, collimator and movable treatment couch. The treatment couch can move in three (x, y, z) directions. Radiation can be delivered to the tumor from any angle by rotating the gantry and moving the treatment couch[32].

Problems

Radiotherapy is a treatment option for pancreatic cancer patients who don't have heart, liver, or kidney dysfunctions or distant metastasis and whose predicted survival is more than 3 mo. Of the pancreatic cancer patients that seek radiotherapy, most have locally advanced unresectable tumors which are large and of irregular shape. It is difficult to give proper radiation doses to such tumors.

Pancreatic tumors have low radiosensitivity and, in order to inhibit or kill tumor cells, large doses are of radiation are needed. However, the pancreas is located behind the peritoneum and near vital organs and important blood vessels such as stomach, intestines, liver, kidney, spinal cord, *etc*. These tissues are very sensitive to radiation and damage to them may lead to serious consequences.

The application of radiotherapy is limited by the high cost and difficult operation of radiotherapy equipment. It is still unknown whether the benefits of this technique outweigh its high cost in patients with locally advanced pancreatic cancer.

Prospects

In future, we should be able to take precise images of pancreatic tumors by nanotechnology and perform conformal radiotherapy using such images. It will also be advantageous to develop more selective radioactive elements, such as radioactive elements against tumor cells or tumor stem cells, and to determine more accurate radiation dosage using biological equivalent dose, hyperfractionation, accelerated hyperfractionation and hypofractionation so as to achieve greater benefit.

INTERVENTIONAL THERAPY

Actualities

Transvascular therapy: As well as regional perfusion of chemotherapy drugs, radiation sources are also used. They are implanted into the tumor to deliver beams of radiation. Studies showed that this method improved therapeutic effect with a total effective rate of 70% (CR + PR), and MST of more than 10 mo. Injection of colloidal[32] phosphorus (P) into solid tumors helped to kill tumor cells and reduced the blood flow to the tumor[33].

Percutaneous puncture (or non-puncture) therapy: Injection of absolute ethanol into tumors is an adjuvant therapy that inhibits the progression of tumor. It is safe and convenient and has led to better prognosis in pancreatic cancer patients whose primary tumor is relatively small but can not tolerate major surgery[34].

To puncture the pancreatic tumor under the guidance of computer tomography (CT) or B type ultrasound, and utilize multi-stage radio frequency or microwave coagulation to dissolve tumor itself was safe, effective and minimally invasive[35].

Resecting or dissolving a tumor or injecting drugs into a tumor could also be performed under endoscopy.

Problems

It is difficult to perform interventional therapy in pa-

tients with pancreatic cancer. Most pancreatic tumors have decreased blood flow. They are supplied by several small blood vessels. The embolic agents often can not reach the nidus. Collateral circulation may appear near the embolized vessel after embolization which makes it difficult to kill the tumor cells. If peripheral vascular embolization material is used, it may enter normal pancreatic tissues through a communicating branch and lead to a disastrous result. CT-guided injection is only suitable for a nidus that can be visualized by CT. It can not be used in a nidus that has the same density as normal tissue. Moreover, the relationship between the dosage of drug and the size of the tumor has not been standardized. Percutaneous puncture may cause damage to the normal organs and may lead to massive hemorrhage if the nidus is located on the edge of the organ or near main vessels. Perfusion chemotherapy is far less effective than arterial perfusion plus embolization.

Although images taken immediately after embolization show that tumor vessels are blocked and the tumor blood supply cut off, images taken later may show some of the vessels become unobstructed or new vessels emerge, indicating the tumor is growing or recurring. In most cases, arterial embolization needs to be performed for at least twice.

Solutions

Biological therapies mainly include gene therapy, immunotherapy and therapies that induce tumor cell apoptosis or inhibit tumor angiogenesis. Gene therapy inserts normal tumor suppressor genes into the patient's tumor cells and replaces deleterious mutant alleles to treat cancer. It is a new treatment option for patients besides surgery, chemotherapy, and radiotherapy. With the use of endosonography, gene therapy or cell-targeted therapy can be performed[35].

With the help of a robot, rather than physician alone, puncture is performed more quickly and accurately, which causes less damage to the surrounding tissues.

Performing interventional therapy under the guaidance of magnetic resonance imaging may avoid the influence of radioactive rays on patients and healthcare workers and minimize the CT scan error on tissues with the same density.

Micro catheter with a laser or catheter ablation system helps to avoid damage caused by percutaneous puncture.

Photodynamic therapy is a medical treatment that administers a photosensitizing drug to the patient and the tissue to be treated is exposed to light suitable for exciting the photosensitizer. The result is an activated oxygen molecule that can destroy nearby cells. It can damage endothelial cells of the tumor vessel, and lead to vascular thrombosis, microcirculatory disturbances, ischemia and necrosis of the tumor[36].

Nanopolymers can be used to wrap chemotherapy drugs, radioactive particles, or biological agents into microspheres, which can be administered into the pancreatic tumor by percutaneous puncture under the guidance of CT or B type ultrasound. Nanoparticles are slowly released and reach a high concentration in the tumor, killing tumor cells and minimizing the damage to the normal tissues.

IMMUNOTHERAPY

Recent developments

Monoclonal antibody therapies: Therapies include pure antibody therapy and conjugated antibody therapy. The former is the use of monoclonal antibodies to bind specifically to tumor antigens, leading to antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity. In conjugated antibody therapy biological engineering technology is used to link the monoclonal antibody with drugs, toxins, radionuclides or enzyme prodrugs to create an entity to kill tumor cells.

MAb 17-1A is an IgG2a antibody created by immunizing mice with the SW1038 colorectal cancer cell line. It binds to the tumor cell surface, activates T-cells and kills tumor cells, as proved in animal experiments. MAb BW-494 is an IgG1 antibody created by immunizing mice with the BALB/C colorectal cancer cell line. It can mediate human monocytes and induce antibody-dependent cellular cytotoxicity against ^{51}Cr labeled pancreatic cells. ^{131}I labeled MAb BW-494 can inhibit the growth of tumor cells in mice with transplanted human pancreatic tumors. MAb YPC3 is an IgG1 antibody created by cell hybridization. Either MAb YPC3 or YPC3-mediated LAK can inhibit the growth of tumors. MAb C017-1A or the C017-1A analog bind the GA 733 antigen expressed in pancreatic tumor cells and induce cytotoxic immune response by antigen-specific proliferation, T cells and delayed-type hypersensitivity. Culture of antinuclear antibody P and several pancreatic tumor cell lines together and the antibody has been found to significantly inhibit the proliferation of pancreatic tumor cells, promote their apoptosis and reduce the tumor size. 425(scFv)-pseudomonas exotoxin A (ETA), a recombinant immunotoxin generated by fusing the anti-EGFR single chain variable fragment 425(scFv) to a truncated mutant of ETA, can significantly reduce the risk of pancreatic cancer metastasis to the lungs in mice. Trials of MAb in combination with chemotherapy showed large doses of chimeric MAb or humanized MAb were well tolerated by patients.

Cytokine immunotherapy: In exogenous cytokine therapy an antitumor cytokine is inserted into the tumor. interleukin (IL)-12 is an important anti-tumor cytokine. Injection of adenovirus encoding IL-12 plus adenovirus encoding MIP3a into tumors induces the generation of cytotoxic T lymphocytes and causes damage to the tumor cells in several ways. Tumor cell apoptosis is induced *via* Fas-pShutle, although the recurrence rate is very high. Giving IL-2 to patients with pancreatic cancer *via* subcutaneous injection before surgery showed improved two-year survival rate compared with the control

group[37]. The *IL-2* gene plus interferon-γ can increase the total amount of $CD4^+$, $CD8^+$ lymphocytes, and induce anti-tumor immune response.

In cytokine-directed therapy, cytokines are conjugated with a toxin, radionuclide, or chemotherapy drug and act on the tumor cells that express the relevant cytokine receptor. IL-13 cytotoxin, composed of IL-13 and ETA, demonstrated antitumor activity in studies of many kinds of tumors. However, IL-13 is differently expressed in various kinds of tumors and its effects is not consistent. Tumor cells that express type I IL-13R may be more sensitive to IL-13 cytotoxin.

In cytokine gene therapy a cytokine gene is inserted into tumor cells resulting in production of cytokine which combats the tumor. After ras17 peptide vaccine combined with granulocyte-macrophage colony-stimulating factor was administered to patients with pancreatic cancer *via* subcutaneous injection, specific CD8 cytotoxic T-lymphocytes that could kill pancreatic tumor cells were detected in peripheral blood mononuclear cells[38]. MALP-2 is a synthetic lipopeptide that can inhibits tumor cells by inducing the synthesis of cytokines and chemokines, as well as the maturation of dendritic cells by toll-like receptor 2 and toll-like receptor 6[39].

Problems

Because pancreatic tumor-specific antigens have not yet been discovered, antigen immunotherapy lacks of specificity. Besides of this, immune escape mechanisms of tumors add to the obstacles to successful immunotherapy. Possible changes in tumor antigens are as follows: defects in tumor antigen and antigen modulation, blocking or coverage of tumor antigens, disorders of tumor antigen processing and presentation, underexpression or missing of major histocompatibility complex (MHC)-1 molecules, dendritic cell dysfunction, abnormal expression of tumor cell costimulatory molecules, overexpression of FasL in tumor cells, induction of $CD4^+CD25^+$ T cells and suppression of antitumor immune response. The effects of monoclonal antibodies and cytokines have not been fully confirmed and high doses of them may not be tolerated by patients.

Solutions

Adoptive cellular immunotherapy: This kind of treatment is used to help the immune system fight against cancer by giving cancer-specific T cells to the patient. It is seldomly used in pancreatic cancer and its therapeutic effect is not confirmed. (1) Adoptive transfer of dendritic cells: In the presence of granulocyte-macrophage colony-stimulating factor, dendritic cells are separated from peripheral blood mononuclear cells of patients with metastatic pancreas cancer, pulsed with supernatant of tumor cells, and administered to the patient by subcutaneous injection. Antitumor T-cells are produced, indicating the significant inhibition of tumors by this therapy[40]. GEM can induce the differentiation of $CD14^+$ and $CD11c^+$ DC and improve the therapeutic effect of GEM in combination with other therapies[41]; and (2) Adoptive transfer of lymphocytes: Allogeneic mixed lymphocytes cultured *in vitro* are injected into pancreatic tumors under the guidance of endoscopic ultrasound. The therapy is found to be effective and has no significant toxicity although controlled studies that involve more samples are needed. Through *in vitro* modification and immunostimulation, lymphocytes may be used as antigen presenting cells to treat pancreatic tumor cells with *p21* and *p53* mutations.

Active immunotherapy: Tumor vaccination may activate or strengthen specific anti-tumor immune response, prevent the growth, spread and recurrence of tumor cells. Tumor vaccines include cell vaccines, peptide vaccines and DNA vaccines. (1) Tumor cell vaccine technology: These vaccines are produced from actual cancer cells that have been removed during surgery. The cells are treated in the lab, usually with radiation, or modified by albumin. They are then injected into the patient. The immune system recognizes antigens on these cells, then seeks out and attacks any other cells with these antigens that are still in the body. Overexpression of heat shock protein in pancreatic tumors can inhibit the apoptosis of tumor cells. Quercetin is a HSP70 inhibitor which inhibits HSP70 in pancreatic tumor cells but not in normal pancreatic cells. Isolated HSP can bind to MHC-l molecules and can be recognized by the immune system. Thus, it can be used as tumor cell vaccine[42]; (2) Molecular vaccine technology: Tumor antigen peptide is synthesized by genetic engineering techniques and combined with the MHC-1 molecule, making it recognizable by antigen presenting cells; and (3) Idiotype antibodies: Primary antibodies, obtained by using tumor antigens to immunize other animals, are utilized to create secondary antibodies, which can be used to activate anti-tumor activity of the immune system.

Suicide genes: Suicide gene therapy is also called drug sensitivity gene therapy, or virus-directed enzyme prodrug therapy. Suicide genes are prodrug converting genes or cytotoxic factor receptor genes from prokaryotes or lower organisms. In animal experiments, suicide genes introduced into tumor cells killed these cells by converting non-toxic or low-toxic prodrugs into toxic metabolites.

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