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BRIEF ARTICLE

Intervention of Mirtazapine on gemcitabine-induced mild cachexia in nude mice with pancreatic carcinoma xenografts

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Abstract

AIM: To investigate the effect of Mirtazapine on tumor growth, food intake, body weight, and nutritional status in gemcitabine-induced mild cachexia.

METHODS: Fourteen mice with subcutaneous xenografts of a pancreatic cancer cell line (SW1990) were randomly divided into Mirtazapine and control groups. Either Mirtazapine (10 mg/kg) or saline solution was orally fed to the mice every day after tumor implantation. A model of mild cachexia was then established in both groups by intraperitoneal injection of Gemcitabine (50 mg/kg) 10 d, 13 d, and 16 d after tumor implantation. Tumor size, food intake, body weight, and nutritional status were measured during the experiment. All mice were sacrificed at day 28.

RESULTS: (1) After 7 d of gemcitabine administration, body-weight losses of 5%-7% which suggested mild cachexia were measured; (2) No significant difference in tumor size was detected between the Mirtazapine and control groups ($P > 0.05$); and (3) During the entire experimental period, food intake and body weight were slightly greater for the Mirtazapine group compared with controls (although these differences were not statistically significant). After 21 d, mice in the Mirtazapine group consumed significantly more food than control mice (3.95 ± 0.14 g *vs* 3.54 ± 0.10 g, $P = 0.004$). After 25 d, mice in the Mirtazapine group were also significantly heavier than control mice (17.24 ± 0.53 g *vs* 18.05 ± 0.68 g, $P = 0.014$).

CONCLUSION: Mild cachexia model was successfully established by gemcitabine in pancreatic tumor-bearing mice. Mirtazapine can improve gemcitabine-induced mild cachexia in pancreatic tumor-bearing mice. It was believed to provide a potential therapeutic perspective for further studies on cachexia.

Key words: Pancreatic carcinoma; Cachexia; Mirtazapine; Gemcitabine; Antidepressant

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INTRODUCTION

Pancreatic cancer is one of the most lethal malignancies as the overall survival rate remains 4% for all stages and

races[1]. Clinical studies have established gemcitabine as the standard treatment for advanced pancreatic cancer. These studies have demonstrated significant clinical benefits (including improved survival) from gemcitabine[2-4]. Unfortunately, there are serious side effects associated with this anti-cancer drug that can adversely affect the patient's quality of life. These include nausea, vomiting, dyspepsia, weight loss, and cachexia.

Cachexia is characterized by major metabolic abnormalities and maladaptations. Often, food/energy intake is reduced, resting energy expenditure is increased, and catabolism is accelerated[5]. Cachexia is associated with anorexia, fat- and muscle-tissue wasting, and a progressive deterioration in the quality of life[6]. As many as 80% of all patients with cancer develop cachexia before death, and in over 20% of these patients, cachexia is the primary cause of death[7-9]. For patients with advanced-stage cancer, 80% suffer from cancer-associated anorexia/cachexia syndrome[10].

Mirtazapine represents a new class of antidepressant drugs. It is a noradrenergic and specific serotonergic antidepressant, which stimulates 5-hydroxytryptamine (HT) 1 receptors, but blocks serotonin 5-HT2/3 and histamine H1 receptors[11]. We have previously shown that 78% of patients with pancreatic cancer also suffer from clinical depression[12]. This figure jumps to 92.3% for patients undergoing chemotherapy. Mirtazapine has the potential to increase appetite and stimulate body-weight gains in these patients[13-15]. Using a mouse model for pancreatic cancer, we previously demonstrated that Mirtazapine increases food intake, enhances body weight, and improves the nutritional status of mice with cancer[16].

A 5% loss of body mass suggests an advanced to mild form of cachexia, whereas losses > 10% suggest severe cachexia[17,18]. Early interventions that treat mild cachexia often lead to substantial quality-of-life benefits for cancer patients. For the study reported herein, we therefore established a mouse model of chemotherapy-induced mild cachexia using gemcitabine and measured the effects of Mirtazapine monotherapy on tumor growth, food intake, body weight, and general nutritional status. These experiments were performed using nude mice implanted with human pancreatic cancer cells.

MATERIALS AND METHODS

Drugs and reagents

Mirtazapine was kindly provided by Organon (Oss, The Netherlands). Gemcitabine was purchased from Eli Lilly and Co. (Indianapolis, IN, United States). RPMI1640 and fetal bovine serum were purchased from Gibco (Grand Island, NY, United States).

Animals

BALB/*c nu/nu* mice were purchased from the Experimental Animal Center, Guangzhou University of Chinese Medicine. Approval for these studies was acquired from the animal-care committee (license number: SCXK 2008-0020). Mice were bred and maintained under pathogen-free conditions in the Animal Center of Sun Yat-Sen University. Mice were housed 4-5 per cage under standard conditions, i.e., 22 ± 1 ℃, ad libitum access to water and standard rat chow, and a 12-h light/dark cycle. Experiments were performed using mice that were 4-6 wk old and 20-22 g.

Pancreatic cancer cell lines and culture conditions

The human pancreatic cancer cell line SW1990 was the kind gift of the Second Affiliated Hospital of Sun Yat-Sen University. Cells were maintained in RPMI-1640 media supplemented with 10% fetal bovine serum (FBS). Monolayer cultures were maintained in culture flasks and incubated under 50 mL/L CO_2 and 950 mL/L O_2 at 37 ℃. Trypsinization was stopped with medium that contained 10% FBS. Cells were then washed once in serum-free medium and resuspended in Hanks' balanced salt solution. Only single-cell suspensions that displayed greater than 90% viability were used for injections.

Establishment of a chemotherapy-induced cachexia model using gemcitabine

The subcutaneous pancreatic cancer model was established using the methods of Jia *et al*[19] with slight modifications. To produce the SW1990 tumor, 3×10^6 cells (in 0.2 mL) were inoculated subcutaneously into the right flank of each nude mouse. Tumor sizes were measured *via* callipering. When the subcutaneous solid tumors reached approximately 1 cm in diameter, they were aseptically removed from the donor animals. Macroscopically visible necrotic tissue was cut away, and the remaining healthy tumor tissue was cut with scissors into pieces that were approximately 1 mm^3. The tumor pieces were placed into Hanks' balanced salt solution that contained 100 units/mL penicillin and 100 mg/mL streptomycin. A small incision was then made through the right dorsal flank of each nude mouse and a piece of tumor was implanted beneath its skin. Chemotherapy-induced mild cachexia was established by intraperitoneal injection of 50 mg/kg gemcitabine on days 10, 13, and 16 after tumor implantation.

Mirtazapine administration

Fourteen mice were randomly assigned to either the Mirtazapine or the control group (7 mice per group). After tumor implantation, Mirtazapine (10 mg/kg) was orally fed to the Mirtazapine group once per day. Normal saline solution was fed to the control group. Chemotherapy-induced mild cachexia was then established in both groups, as described above. Animals were sacrificed after 28 d.

Measurements

The transplanted tumor sizes were measured using a Vernier caliper every fourth day, and tumor volume (V) was calculated as: $V = w^2 \times l/2$, where w is the width and l is the length of the tumor[20]. Mice were sacrificed on day 28 after tumor transplantation, and the tumors were then removed. Both the tumors and the mice carcasses were then weighed. During the experiment, body weight was

Table 1 Effect of Mirtazapine on body weight and nutritional status

Nutritional status	Group	Baseline	5 d	9 d	13 d	17 d	21 d	25 d	28 d
Body weight (g)	Control	21.64 ± 0.96	21.51 ± 0.89	21.20 ± 0.73	20.86 ± 0.71	20.15 ± 0.67	18.70 ± 0.58	17.24 ± 0.53	16.04 ± 0.66
	Mirtazapine	21.75 ± 0.75	21.69 ± 0.79	21.59 ± 0.75	21.14 ± 0.52	20.50 ± 0.50	19.13 ± 0.55	18.05 ± 0.68	16.89 ± 0.73
	P value	0.783	0.654	0.282	0.386	0.266	0.151	0.014	0.017
Subcutaneous fat (mm)	Control	0.74 ± 0.14	0.72 ± 0.14	0.70 ± 0.13	0.69 ± 0.09	0.66 ± 0.09	0.60 ± 0.10	0.50 ± 0.10	0.41 ± 0.07
	Mirtazapine	0.71 ± 0.12	0.70 ± 0.11	0.70 ± 0.10	0.69 ± 0.10	0.68 ± 0.10	0.63 ± 0.10	0.52 ± 0.09	0.44 ± 0.08
	P value	0.691	0.773	0.928	0.938	0.845	0.697	0.708	0.548
Arm circumference (mm)	Control	19.45 ± 1.21	19.03 ± 0.81	18.29 ± 0.88	17.24 ± 0.52	16.00 ± 0.62	15.13 ± 0.68	13.76 ± 0.65	13.06 ± 0.52
	Mirtazapine	19.52 ± 0.88	19.20 ± 0.73	18.51 ± 0.65	17.58 ± 0.67	16.27 ± 0.67	15.31 ± 0.68	14.04 ± 0.54	13.25 ± 0.53
	P value	0.901	0.694	0.619	0.323	0.482	0.621	0.424	0.566

Table 2 Effects of Mirtazapine on tumor size, pancreatic tumor weight and food intake

Effects on tumor size (mL)							
Group	5 d	9 d	13 d	17 d	21 d	25 d	28 d
Control group	37.67 ± 7.57	62.59 ± 24.06	105.39 ± 19.92	174.77 ± 15.16	258.54 ± 20.98	365.58 ± 17.63	472.62 ± 13.03
Mirtazapine group	37.12 ± 10.55	58.09 ± 26.00	100.21 ± 21.87	171.57 ± 16.94	246.88 ± 25.64	357.80 ± 15.75	466.95 ± 14.21
P value	0.926	0.748	0.638	0.726	0.376	0.411	0.454
Effects on pancreatic tumor weight (g)							
Group	Mice body weight (Tumor-bearing) (g)		Mice body weight (Tumor removed) (g)		Tumor weight (g)	*P* value	
Control group	16.04 ± 0.66		15.61 ± 0.59		0.42 ± 0.09	0.35	
Mirtazapine group	16.89 ± 0.73		16.51 ± 0.63		0.37 ± 0.11		
Effects on food intake							
Group	Basic line	7 d	14 d	21 d	28 d		
Control group	5.15 ± 0.12	5.13 ± 0.13	4.21 ± 0.10	3.54 ± 0.10	3.02 ± 0.16		
Mirtazapine group	5.17 ± 0.15	5.19 ± 0.14	4.41 ± 0.16	3.95 ± 0.14	3.57 ± 0.11		
P value	0.917	0.544	0.054	0.004	0.003		

measured every forth day. Food intake was expressed as daily consumption in grams per animal weekly. The rate of weight loss was calculated as: weight loss (%) = (1-body weight$_{timepoint}$/body weight$_{base\text{-}line}$) × 100%. A weight loss > 5% suggested the development of mild cachexia[17,18]. Abdominal skin-fold and arm diameter were measured using the caliper every third day. Subcutaneous fat was calculated as: subcutaneous fat (mm) = skin-fold thickness × 0.5. Arm circumference was calculated as: arm circumference (mm) = diameter × 3.14.

Statistical analysis

Statistical analyses were performed using SPSS 13.0 for Windows. Data were expressed as mean ± SD, and were compared using one-way analysis of variance and the Student-Newman-Keuls test for multiple comparisons between groups. Tumor inhibition rates were compared using the χ^2 test. Differences were considered statistically significant for $P < 0.05$ using two-tailed tests.

RESULTS

Establishment of a model for chemotherapy-induced mild cachexia using gemcitabine

Seven days after the first gemcitabine injection, body weight in the control group had declined from 21.64 ± 0.96 g to 20.15 ± 0.67 g (a 6.89% decrease) (Table 1). A similar decline was measured for the Mirtazapine group: 21.75 ± 0.75 g to 20.50 ± 0.50 g (a 5.75% decrease). A mild form of cachexia had therefore been established, indicating that the administration of gemcitabine (50 mg/kg) for 1 wk could induce mild cachexia in mice that carried a pancreatic tumor.

Effect of Mirtazapine on tumor growth

As the experiment progressed, small increases in the sizes of the tumors were regularly measured (Table 2). Similar rates of tumor growth were evident in both the Mirtazapine and control groups, however, statistically significant differences in tumor size were never detected between the two groups.

Tumor weight was measured at 28 d, immediately after the mice were sacrificed. Again, a statistically significant difference between the Mirtazapine and control groups concerning tumor weight was not detected (0.37 ± 0.11 g *vs* 0.42 ± 0.09 g, $P > 0.05$). It was indicated that gemcitabine had inhibitory effect on pancreatic cancer growth, which could not be apparently strengthened by Mirtazapine.

Effect of Mirtazapine on daily food intake

Following the administration of gemcitabine, daily food intake gradual declined in both groups (Table 2). By day 21 of the experiment, however, mice given Mirtazapine were eating more food than did the controls (3.54 ± 0.10 g *vs* 3.95 ± 0.14 g, $P < 0.01$). This effect was also seen at the end of the experiment (day 28) (3.02 ± 0.16 g *vs* 3.57 ± 0.11 g, $P < 0.01$), demonstrating that Mirtazapine can slow the reduction in food intake caused by chemotherapy.

Effect of Mirtazapine on body weight and nutritional status

At the beginning of the study, mice from the two groups

had similar average body weights ($P > 0.05$). Throughout the course of the experiment, mice in both groups exhibited a gradual decrease in body weight (Table 1). During initial stages of the experiment, the control group seemed to lose slightly more weight than did the Mirtazapine group, although these differences were not statistically significant ($P > 0.05$). At day 25, however, mice fed Mirtazapine were significantly heavier than control mice (18.05 ± 0.68 g *vs* 17.24 ± 0.53 g, $P = 0.014$). This phenomenon was also seen at 28 d suggesting that early Mirtazapine interventions can ameliorate the weight loss that is typically associated with chemotherapy (e.g., gemcitabine).

Subcutaneous fat and arm circumference were also measured for the two groups of mice (Table 1). For both groups these measured parameters gradually decreased during the course of the experiment. The data suggest that slower reductions were taking place in the Mirtazapine group (compared with the control group), but statistically significant differences were not detected ($P > 0.05$).

DISCUSSION

Cachexia is a disease process that develops in numerous chronic and end-stage pathologies. Clinical manifestations of cachexia include weight loss, anorexia, fatigue, muscle wasting, aesthesia, anemia, and edema. Particularly strong correlations between cachexia and solid tumors of the upper gastrointestinal tract have been described. It is estimated that 83% of pancreatic cancer patients suffer from cachexia during the course of their disease[17]. In addition, patients with pancreatic cancer have the highest incidence of weight loss (83%-87%), with about 30% reporting a weight loss of > 10%[21,22].

To experimentally dissect cachexia, a variety of cachexia models have been established. Murine colon-26 adenocarcinoma cells, Yoshida ascites hepatoma (AH-130) ascites hepatoma cells, and several other cachexigenic cell lines (JHU012, JHU022, and MAC1) have been used to establish different cachexia models[23-25]. The administration of chemotherapy drugs, however, has only rarely been used to generate mild cachexia. Gemcitabine is an extremely effective chemotherapy agent that inhibits the growth of cancerous tumors. Unfortunately, this drug is also associated with a number of adverse side effects, which include nausea, vomiting, loss of appetite, weight loss, and cachexia[26,27]. For the study reported herein, we injected nude mice with Gemcitabine to induce cachexia. Significant weight loss was observed in these animals, suggesting that a model for mild cachexia had been established.

Potential treatments for cancer cachexia (e.g., megestrol acetate, testosterone, growth hormone, or ghrelin) have been the subject of intense research recently. One study suggested that progestogens (e.g., megestrol acetate, or medroxyprogesterone) should be preferentially used to treat anorexia in patients with cancer because of toxic side effects associated with corticosteroids[17]. Several studies have demonstrated that ghrelin, which is a peptide found in both the brain and gut and stimulates food intake, may ameliorate cancer cachexia[9,28]. To date, however, there are no consistent opinions or guidelines that support the use of one therapeutic agent over another.

Mirtazapine represents a novel antidepressant and has been shown to cure insomnia, depression, and anxiety, but it is unclear if it also stimulates appetite and improves the nutritional status of patients[29-32]. We have previously shown that a 6-wk administration of Mirtazapine in a murine model of pancreatic cancer increased food intake and body weight by 16.39% and 8.39%, respectively. These nutritional improvements were significantly better than was seen with other antidepressants[16]. Our previous work had also shown that gemcitabine induces cachexia. In the current study, therefore, we investigated whether an early Mirtazapine intervention could ameliorate the mild cachexia associated with gemcitabine (50 mg/kg) administration in mice that bear pancreatic tumors. Mirtazapine significantly improved both food intake and body weight of these mice, although losses in subcutaneous fat and skeletal muscle were not slowed. The reason for these fat and muscle losses may be that Mirtazapine does not affect lipolysis or the adenosine triphosphate/ubiquitin/proteasome system, both of which are upregulated in cachexia. In the future, therefore, it will be important to determine the dose-effect relationship between Mirtazapine and chemotherapy-induced cachexia. We will also test whether enhanced nutritional improvements can be obtained *via* combinatorial treatments that include Mirtazapine and megestrol acetate or ghrelin.

In summary, for the first time, chemotherapy-induced mild cachexia has been established in a murine model of pancreatic cancer using gemcitabine. In addition, our results demonstrate that early administration of Mirtazapine may represent an effective treatment for both chemotherapy- and cancer-related cachexia. Future experiments that use larger groups of animals and long-term courses of treatment will be necessary to confirm these findings. Clinical tests in cancer patients are also needed.

COMMENTS

Background

Gemcitabine is commonly used to treat pancreatic cancer. This anti-cancer drug, however, is often associated with side effects (e.g., nausea, vomiting, dyspepsia, weight loss, and cachexia) that adversely affect the patient's quality of life. Mirtazapine may increase appetite and weight gain, thereby ameliorating cachexia in this context.

Research frontiers

Mirtazapine can significantly increase the food intake, enhance the body weight and improve the nutritional state in a pancreatic cancer mouse model in the authors' previous researches. In this study, the authors do the advanced research to find whether Mirtazapine could also show positive effects on improvement of appetite loss and weight loss which were the main features of cachexia.

Innovations and breakthroughs

The research shows that Mirtazapine improved gemcitabine-induced mild cachexia in mice that bear pancreatic tumors.

Applications

Mirtazapine represents a new class of antidepressant that may also positively affect appetite and weight gain. These results suggest novel therapeutic applications for Mirtazapine, and will help direct future studies concerning cachexia.

Peer review

This is an interesting research that the authors utilized gemcitabine to induce

mild cachexia in mice with pancreatic tumors and found that Mirtazapine improved the symptoms associated with mild cachexia. These findings identify a novel means of treating cachexia, although additional experiments, both in the lab and in the clinic, are necessary before this strategy can be widely applied to cancer patients.

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