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Original Article

Efficacy of DMBG and gemcitabine as a combination treatment on advanced pancreatic cancer, and their effect on miR-190, miR-196a, miR-221 and miR-222

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Abstract: Objective: The study was designed to assess the efficacy of DMBG and gemcitabine as a combination treatment for advanced pancreatic cancer. Methods: A retrospective analysis was conducted for clinical samples from 65 patients admitted to our hospital due to advanced pancreatic cancer, after which, they were divided into 2 groups based on the date of admission. The control group (n=33) was treated with gemcitabine and the observation group (n=32) was treated with DMBG and gemcitabine. The two groups were compared for DCR, survival, incidence of toxic reactions, QOL and levels of 4 miRNAs after treatment. Results: (1) DCR in the observation group was 78.12% and in the control group was 54.55% (P<0.05); (2) after treatment, patients in the observation group maintained survival without PD and an overall survival of (4.15±1.19) months and (7.58±2.42) months, respectively; while those in the control group survived (3.32±0.86) months and (5.43±1.37) months (P<0.05); (3) no statistical difference was observed between the two groups in terms of incidences of various toxic reactions (P>0.05); (4) treatment resulted in a KPS score and a ZPS score of (84.23±7.49) and (0.44±0.07) in the observation group, and (72.80±6.92) and (0.72±0.11) in the control group (P<0.05); (5) miR-190, miR-196a, miR-221 and miR-222 levels were (2.03±1.05), (2.41±1.26), (2.65±1.38), and (1.72±0.76) in the observation group, and (2.84±1.23), (3.89±1.41), (4.02±1.73) and (2.51±0.95) in the control group (P<0.05). Conclusion: DMBG and gemcitabine as a combination treatment show values in patients with advanced pancreatic cancer, which can elevate the DCR, prolong the survival time, improve QOL and ensure treatment safety.

Keywords: Advanced pancreatic cancer, DMBG, gemcitabine, miRNA, survival time

Introduction

As one of the most common malignant tumors of digestive tract, pancreatic cancer is not identified in most cases until the middle and advanced stages because of insufficient clinical manifestations in early stages [1]. Patients with advanced pancreatic cancer are characterized by a high grade of malignancy and a short survival. Differing from malignant tumors such as gastric cancer and lung cancer, pancreatic cancer progresses rapidly regardless of its short course, and its complete resection rate is only about 10% though patients have a chance for surgical resection treatment. Therefore, an extremely high case fatality rate (CFR) is related to pancreatic cancer [2].

Clinically, chemotherapy is a dominating means of treating advanced pancreatic cancer. Although chemotherapy can effectively kill cancer cells, slow down the progression of the disease, and prolong the patient's survival rate; because of the obvious cytotoxicity of the chemical drugs, continuous chemotherapy can significantly reduce the immune functions of patients, thus leading to toxic side effects that significantly affect the quality of life (QOL) of patients. Hence, it is very important to choose a reasonable chemotherapeutic drug [3]. Gemcitabine has been verified extensively for its efficacy as a widely applied drug in chemotherapy. However, it is known that when the drug kills cancer cells, normal cells are also damaged, resulting in reduction of white blood cells and clear toxic reactions including nausea and vomiting [4]. It is believed from this study that gemcitabine combined with other drugs could improve the efficacy and reduce the toxicity, but

clinically few studies have been carried out on gemcitabine combined application. This study focuses on seeking effective drugs that can be combined with gemcitabine, so as to assist advanced pancreatic cancer to be more effectively controlled, increase the survival rate, prolong the survival time and improve the QOL of patients.

This study included 65 patients with advanced pancreatic cancer from our hospital, who were divided into the control group for treatment with Gemcitabine, and the observation group for treatment with Gemcitabine in combination with DMBG, respectively; in order to find more effective and safe drugs for the treatment of advanced pancreatic cancer.

Material and methods

Materials

A retrospective analysis was conducted with 65 patients admitted to our hospital due to advanced pancreatic cancer, after which, they were divided into 2 groups based on the date of admission. The control group included 33 patients aged between 41 and 70, and the observation group included 32 patients aged between 40 and 72. (1) Inclusion criteria: patients must fit with the diagnosis standards of pancreatic cancer [5]; be in advanced stage where they are not suitable for surgical treatment or when the tumor has undergone widespread metastasis; with one or more measurable lesions; have never received treatment with the drugs studied herein; patients have agreed with the study (or guardians), and informed consent was signed. This study has been approved by the Ethics Committee. (2) Exclusion criteria: patients who fail to satisfy the inclusion criteria; patients with expected survival time of less than 3 months; patients with other malignant tumors; patients with severe diseases in the heart, liver, kidney and lung systems; and patients who were allergic to the drugs studied were also excluded.

Methods

Patients from the control group were administrated Gemcitabine via intravenous drip at a dose of 1000 mg/m^2 on d1, d8 and d15. The treatment was repeated at an interval of 4 weeks.

Patients from the observation group were administered DMBG orally at a dose of 500 mg each time, three times a day, gemcitabine via intravenous drip at a dose of 1000 mg/m^2 on d1 and d8, and CDDP via intravenous drip at a dose of 30 mg/m^2 from d1 to d3. The treatment was repeated at an interval of 3 weeks.

Blood sugar level (BSL) was measured every day before breakfast during the treatment, and was also measured immediately in the event of discomfort. Symptomatic treatment was carried out on the patients with hypoglycemia. Hypoglycemia was defined as BSL<2.8 mmol/L. Patients in both groups were treated for more than 2 cycles. If the tumor progressed during the treatment, or if there was serious toxic side effects, symptomatic treatment is carried out immediately. Patients who were not relieved could choose to cancel the treatment.

Observation indices

Disease control rate (DCR): all patients completed the treatment successfully, and were assessed for disease control effect in the end according to response evaluation criteria in solid tumors (RECIST) [6]. The results were graded as complete remission (CR) when all lesions disappeared for more than 1 month; partial remission (PR) that lesions reduced by 50% in volume for more than 1 month; stale disease (SD) that the tumor lesion reduced or increased by less than 25% without new lesion; progress disease (PD) that the tumor lesion increased by 25% in volume with new lesions. DCR=CR+PR+SD.

Survival: the two groups were compared for progression free survival (PFS) and overall survival (OS).

Toxic and adverse reaction: the two groups were recorded and compared for toxic reactions after treatment by NCI-CTC 2.0 [7], including anemia, neutropenia, thrombocytopenia, hemorrhage, nausea and vomiting, diarrhea, albuminuria, hematuresis, peripheral neurotoxicity, astriction, and weakness.

QOL: patients' QOL was judged according to results of KPS (Karnofsky) [8] and Zubrod-ECOG-WHO (ZPS) [9]. KPS adopted a centesimal system. Patients with a score above 80 were independent with self-care ability; patients

Table 1. Comparison between the Observation Group and Control Group in General Materials ($\overline{X}$ ± s)/[n (%)]

Materials		Observation Group (n=32)	Control Group (n=33)	t/X^2	*P*
Gender	M	18 (56.25)	17 (51.52)	0.147	0.702
	F	14 (43.75)	16 (48.48)		
Age		53.65±8.79	54.76±9.34	0.493	0.624
Height (cm)		168.57±12.43	164.81±14.72	1.111	0.271
Body weight (kg)		64.53±4.89	65.94±5.21	1.124	0.265
TNM installment		23 (71.88)	25 (75.76)	0.127	0.722
		9 (28.13)	8 (24.24)		
Pathological parting	Duct cell carcinoma	25 (78.13)	24 (72.73)	0.255	0.614
	Acinar cell carcinoma	7 (21.87)	9 (27.27)		
Onset part	Carcinoma of head of pancreas	20 (62.50)	19 (57.58)	0.362	0.529
	Carcinoma of tail of pancreas	10 (31.25)	11 (33.33)		
	Total pancreatic cancer	2 (6.25)	3 (9.09)		

with a score between 50 and 70 were semi-independent with semi-self-care ability; patients with a score under 50 were dependent, requiring assistance. Generally, a score over 80 represented positive postoperative conditions and longer survival, while a score under 60 rendered some tumor treatments impossible. ZPS was based on a 5-score system, in which, 0 indicated normal activities, 1 is mild symptoms with ability to be involved in mild physical activities, 2 is tolerable tumor syndromes with self-care ability and time in bed reduced by half in the daytime, 3 is severe syndromes with more than half of the daytime spent in bed, but the patients could get out of bed, stand up, and take care of them self sometimes, 4 is severe disease that the patient was completely bedridden, and 5 is death. In this study, a higher KPS and a lower ZPS were indications of better QOL.

miRNA: the two groups were measured for the levels of miR-190, miR-196a, miR-221 and miR-222 before and after treatment by methods as follows. Ten ml plasma was drawn with anticoagulant tube and centrifuged for 10 min at 1200 RPM. The liquid supernatant was recycled with a RNA-free test tube, and centrifuged for 10 min at 1500 RPM, after which, the liquid supernatant was collected into a new RNA-free test tube, and stored at 80°C. Total RNA extraction was done with 300 μl plasma according to the instructions in the mirVana PARIS Kit and assayed for RNA purity and concentration with ultraviolet spectrophotometer. cDNA was synthesized by reverse transcription, and miR-190, miR-196a, miR-221 and miR-222 were amplified by SYBR Green method on a real-time PCR amplification instrument. The amplification method was as follows: 50°C, 2 min; 95°C, 5 min; 3× (94°C, 30 s→61°C, 60 s)→37× (94°C, 10 s→60°C, 30 s: collecting the fluorescent), the reaction system was set at 30 μL. The result was read according to the instrument instruction.

Statistical analysis

Statistical analysis was performed with SPSS 22.0. Numerical data was expressed as Mean ± Standard Deviation, comparison studies were carried out through independent-samples T test for data which were normally distributed, and Mann-Whitney U test for data which were not normally distributed, paired test for pre-and-pro comparison in the group; in case of nominal data expressed as [n (%)], comparison studies were carried out through X^2 test for intergroup comparison. $P<0.05$ was considered as statistically significant.

Results

Comparison of general measures in the two groups

No statistically significant difference was observed between the observation group and control group in terms of proportion of male and female patients, age, height, body weight, TNM installment, parting and onset location ($P>0.05$) (**Table 1** and **Figure 1**).

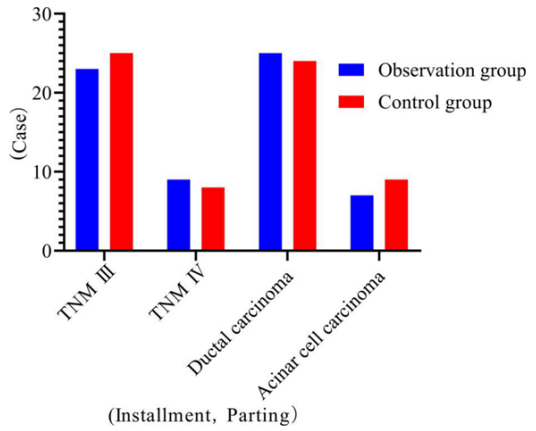

Figure 1. TNM Installment and pathological parting of observation group and control group TNM. No significant difference was observed between the observation group and the control group in proportion of patients at TNM III, TNM IV, with duct cell carcinoma and acinar cell carcinoma (P>0.05).

Comparison of DCR in two groups

Patients in the observation group had 2 cases of CR, 9 case of PR, 14 cases of SD and 7 cases of PD, with DCR of 78.12%; while in the control group there were 0 case of CR, 6 cases of PR, 12 cases of SD, 15 cases of PD, with a DCR of 54.55%. Statistical significance was observed between the two groups in DCR ($P<0.05$) (**Table 2** and **Figure 2**).

Comparison of survival in the two groups

After treatment, PFS and OS in the observation group were (4.15±1.19) months and (7.58±2.42) months, while those of in the control group were (3.32±0.86) months and (5.43±1.37) months, respectively; which were statistically significant ($P<0.05$) (**Table 3**).

Comparison of incidence of toxic reactions in the two groups

No statistical difference was observed between the observation group and the control group in terms of the incidences of various toxic reactions including anemia, neutropenia, thrombocytopenia, hemorrhage, nausea and vomiting, diarrhea, albuminuria, hematuresis, peripheral neurotoxicity, astriction, and weakness ($P>0.05$) (**Table 4**).

Comparison of QOL in two groups

There was no statistical difference in KPS and ZPS scores between the observation group and the control group before treatment ($P>0.05$). After treatment, the observation group attained a KPS of (84.23±7.49), which was significantly higher than the control group of (72.80±6.92); and a ZPS of (0.44±0.07), which was significantly lower than the control group of (0.72±0.11) ($P<0.05$) (**Table 5** and **Figure 3**).

Comparison of miRNA levels in two groups

Significant differences ($P<0.05$) were observed between the observation group and the control group in levels of miR-190, miR-196a, miR-221, and miR-222, which were (2.03±1.05), (2.41±1.26), (2.65±1.38), (1.72±0.76), respectively; and (2.84±1.23), (3.89±1.41), (4.02±1.73), (2.51±0.95), respectively (**Table 6** and **Figure 4**).

Discussion

Pancreatic cancer is characterized by a high grade of malignancy and low survival rate, which, according to statistic data, is only 7%-8% in 5 years for patients with advanced pancreatic cancer [10]. In recent years, development in medical technology allows surgical resection of the tumor in early stages with less postoperative complications and extended survival. However, most patients miss the chance as the disease does not show particular clinical manifestations until the middle and advanced stages, when chemotherapy remains the mostly useful treatment.

Gemcitabine is a drug widely applied in chemotherapy treatment, it works by transforming into active diphosphate and triple phosphate after the action of nucleoside kinase [11]. Gemcitabine diphosphate can effectively suppress the activity of ribonucleotide reductase, and significantly reduce dNTP required in DNA synthesis [12]. Furthermore, gemcitabine triphosphate and dNTP can enter the DNA chain via competitive functions, while the decrease in cell dNTP promotes the penetration of gemcitabine triphosphate into DNA [13]. Meanwhile, studies have proved that DNA polyase ε can neither remove gemcitabine triphosphate which has penetrated into DNA nor repair the extended DNA chain. Therefore, DNS synthesis was blocked and apoptosis was induced [14]. Though the effect of gemcitabine in chemotherapy has been extensively supported [15, 16], it's obvious toxic and adverse effects can't be

Table 2. Comparison between Observation Group and Control Group in DCR [n (%)]

Group	CR	PR	SD	PD	DCR
Observation Group (n=32)	2 (6.25)	9 (28.13)	14 (43.75)	7 (21.88)	25 (78.12)
Control Group (n=33)	0 (0.00)	6 (18.18)	12 (36.36)	15 (45.45)	18 (54.55)
X^2					4.034
P					0.045

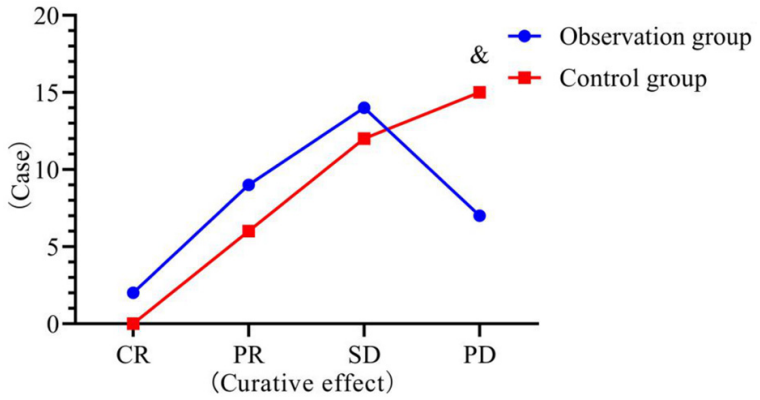

Figure 2. Comparison between observation group and control group in DCR. No significant difference was observed between the control group and the observation group in number of CR, PR, and SD patients (P>0.05). Observation group reported fewer cases of PD patients as compared with the control group (P<0.05). &indicates P<0.05, when PD values are compared in two groups.

Table 3. Comparison between Observation Group and Control Group in PFS and OS ($\overline{X}$ ± s, month)

Group	Number of Case	PFS	OS
Observation Group	32	4.15±1.19	7.58±2.42
Control Group	33	3.32±0.86	5.43±1.37
t		3.230	4.425
P		0.002	0.000

Table 4. Comparison between Observation Group and Control Group in Incidence of toxic reactions [n (%)]

Toxic Reactions	Observation Group (n=32)	Control Group (n=33)	X^2	*P*
Anemia	2 (6.25)	3 (9.09)	0.185	0.667
Weakness	4 (12.50)	3 (9.09)	0.197	0.658
Astriction	2 (6.25)	1 (3.03)	0.383	0.536
Peripheral neurotoxicity	1 (3.13)	2 (6.06)	0.318	0.573
Hematuresis	0 (0.00)	1 (3.03)	0.985	0.321
Albuminuria	0 (0.00)	0 (0.00)	/	/
Diarrhea	1 (3.13)	2 (6.06)	0.318	0.573
Nausea and vomiting	3 (9.38)	2 (6.06)	0.251	0.616
Haemorrhage	0 (0.00)	0 (0.00)	/	/
Thrombocytopenia	1 (3.13)	2 (6.06)	0.318	0.573
Neutropenia	2 (6.25)	1 (3.03)	0.383	0.536

neglected. Therefore, it is very important for a highly effective and low toxic auxiliary therapeutic drug to be combined with gemcitabine.

A number of studies have found that, DMBG, an important drug for diabetes, can not only control BSL, but also play an important role in reducing the onset risk of pancreatic cancer and improving the QOL of patients with pancreatic cancer [17, 18]. DMBG's direct antitumorigenic effect was also established in studies which can targetedly control signal pathways associated with tumor development, effectively regulate autophagy, energy metabolism, ribosomal biosynthesis and mRNA translation for the purposes of controlling cell replication in mammals, and inhibit the development and induced autophagy of fat, development and progression of tumors [19, 20]. The observation group received DMBG treatment on the basis of gemcitabine and yielded a DCR of 78.12%, which was significantly higher than the control group with only treatment with gemcitabine (*P*<0.05). Lyn-Cook B D et al [21] also had the same finding in their study that combination treatment with DMBG can increase the total clinical effective rate of pancreatic cancer as compared with control group subject to chemotherapy, a routine treatment. Moreover, the observation group excelled

Table 5. Comparison between Observation Group and Control Group in QOL before and after Treatment ($\overline{X}$ ± s, score)

Group	KPS		ZPS	
	Before Treatment	After Treatment	Before Treatment	After Treatment
Observation Group (n=32)	68.76±5.26	84.23±7.49	1.86±0.13	0.44±0.07
Control Group (n=33)	67.89±5.41	72.80±6.92	1.79±0.16	0.72±0.11
t	0.657	4.715	1.932	12.200
P	0.514	0.000	0.058	0.000

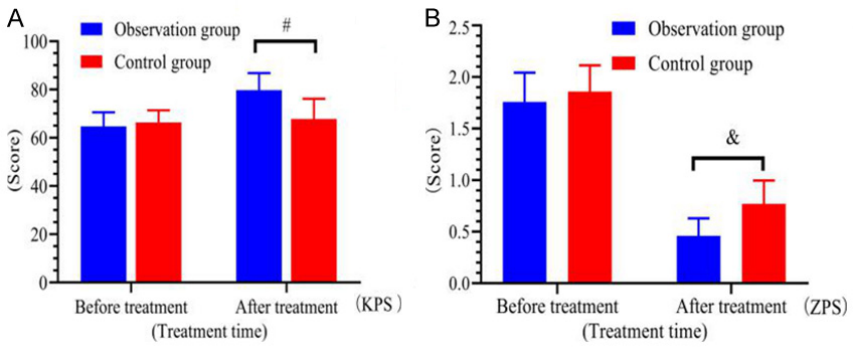

Figure 3. Comparison between observation group and control group in QOL. KPS score in the observation before treatment had no significant difference compared with that in the control group (P>0.05), while that in the observation group after treatment was significantly higher than that in the control group (P<0.05). ZPS score in the observation before treatment had no significant difference compared with that in the control group (P>0.05), while that in the observation group after treatment was significantly lower than that in the control group (P<0.05). #indicates P<0.05 in the comparison of KPS scores between two groups after treatment. &indicates P<0.05 in the comparison of ZPS scores between two groups after treatment.

Table 6. Comparison between Observation Group and Control Group in miRNA Level after Treatment ($\overline{X}$ ± s)

Group	Number of Case	miR-190	miR-196a	miR-221	miR-222
Observation Group	32	2.03±1.05	2.41±1.26	2.65±1.38	1.72±0.76
Control Group	33	2.84±1.23	3.89±1.41	4.02±1.73	2.51±0.95
t		2.851	4.457	3.523	3.695
P		0.006	0.000	0.001	0.001

compared to the control group in terms of PFS, OS, KPS and ZPS (*P*<0.05), indicating that gemcitabine and DMBG as a combination treatment can significantly control the progression of tumors, extend the survival of patients, and improve the QOL. The treatment of the two drugs complement each other and support each other to achieve the ultimate goal of inhibiting the cell growth in connective tissue proliferation areas, of which gemcitabine acts on about 360~570 μm near to the connective tissue proliferation area, and DMBG restructures astrocytes via tumor-associated macrophages (TAM) [22].

After treatment, the observation group demonstrated no significant difference compared with the control group in terms of incidences of anemia, neutropenia,thrombocytopenia, hemorrhage, nausea and vomiting, diarrhea, albuminuria,hematuresis,peripheral neurotoxicity, astriction, and weakness (*P*>0.05), showing that DMBG will not affect the overall treatment safety nor enhance any toxic reactions. In patients with advanced pancreatic cancer, the concentrations of miR-190, miR-196a, miR-221, and miR-222 will be increased, so the levels of various indicators will be significantly increased. Moreover, it is found that the level of indicators is associated with the severity of advanced pancreatic cancer. Therefore, controlling the level of these indicators plays an important role in delaying the disease progression of patients. In the present study, the levels of miR-190, miR-196a, miR-221, and miR-222 in the observation group after treatment were significantly lower than those of in the control group (*P*<0.05), which proves that the combination treatment with DMBG can more significantly improve miRNA levels. Studies have revealed that a miRNA molecule can be bound with hundreds of target mRNAs with different functions

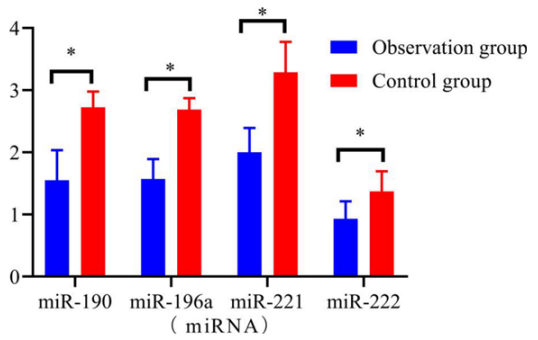

Figure 4. Comparison between the observation group and the control group in miRNA levels after treatment. The observation group demonstrated a lower level of miR-190, miR-196a, miR-221 and miR-222 ($P<0.05$) after treatment as compared with the control group. *indicates $P<0.05$ in the comparison of the same indicators between two groups.

for regulation. miRNA participates in most pathological mechanisms and physiological activities of mammals, and it is vital to the development and progression of a large number of diseases [23]. Therefore, the control of miRNA levels is very important in treatment.

The re-expression of DMBG via some miRNAs can reduce the expression of specific genes of stem cells in patients with pancreatic cancer resistant to gemcitabine, inhibit cell self-healing, clonogenicity, generation and clone formation, promote the cloning and decomposition and cut off the survival of pancreatic cancer cells for the ultimate goal of apoptosis [24].

In conclusion, DMBG and gemcitabine as a combination treatment can significantly reduce the levels of miR-190, miR-196a, miR-221, and miR-222, control disease progression, extend patients' survival and improve their QOL without obvious impact on treatment safety. This treatment shall be extensively applied. However, the present study only contained 2 groups with less study subjects and indices for analysis, resulting in incomprehensive results. In further studies, more attention shall be paid to group numbers, sample size and study coverage, so as to provide more guiding information for clinical treatment of advanced pancreatic cancer.

Disclosure of conflict of interest

None.

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