

The Safety and Therapeutic Effect Analysis of Intraoperative Intraperitoneal Chemotherapy with Lobaplatin for Hepato-Biliary-Pancreatic Cancer

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Research

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Abstract

Background

To examine the safeness and efficacy of intraoperative intraperitoneal perfusion chemotherapy with lobaplatin on hepato-biliary-pancreatic cancer.

Methods

Clinical data were retrospectively collected from a total of 66 patients with HBP cancer undertaken surgeries. They were divided into two groups: the study (lobaplatin) group (33 patients) and the control group (33 patients). The disease-free survival rate, postoperative complications, and chemotherapy side effects (bone marrow, liver, and kidney toxicity) were analyzed to examine the safeness and efficacy of intraoperative intraperitoneal chemotherapy with lobaplatin.

Results

In the study group, two patients had a postoperative subphrenic infection and increased peritoneal effusion, one patient had postoperative leukopenia and thrombocytopenia, while the control group had postoperative abnormal coagulation function in 1 patient, and gastrointestinal bleeding in 1 patient, no significant difference in postoperative complication was observed between the two groups. There was no significant difference in the liver and kidney function between the two groups after surgery ($p > 0.05$). A total of 26 patients in the two groups had recurrence or metastasis within one year after surgery, including eight patients in the study group and 18 patients in the control group. The recurrence rate of hepatocellular cancer in the lobaplatin group and control was 21.14% and 60%, respectively ($P = 0.012 < 0.05$). But there was no significant difference in the disease-free survival function analysis ($P = 0.127 > 0.05$).

Conclusions

Intraperitoneal perfusion chemotherapy with lobaplatin is a safe and effective treatment in the process of radical resection of hepato-biliary-pancreatic tumors, which has therapeutic potential in reducing postoperative tumor recurrence and metastasis.

Background

Hepato-biliary-pancreatic (HBP) cancer is one of the most common life-threatening malignancies worldwide [1]. Despite the enormous progression in the diagnosis and therapy of HBP cancer over the past 20 years, cancer metastasis and recurrence remain the main reasons for the poor disease prognosis of HBP cancer [2, 3, 4]. Currently, surgical resection is the primary treatment of HBP cancer [5, 6]. However,

it is not the perfect treatment method due to the complexity of the disease progression on patients. Patients with HBP cancer may have progressed further after diagnosis and before treatment. The large tumor volume of advanced HBP cancer also increases the incidence of intraperitoneal metastasis of tumor cells [2, 3, 4]. Certain serious complications of HBP cancer, such as tumor rupture and hemorrhage, significantly increase the risk of intraperitoneal tumor cell implantation and metastasis. Therefore, comprehensive treatment is emerging as a critical approach to improve the long-term efficacy of HBP cancer therapy.

In recent years, intraperitoneal chemotherapy provides more strategies for preventing intraperitoneal tumor cell implantation and metastasis [7]. As emerging evidence suggests that intraperitoneal chemotherapy is an effective therapeutic and preventive strategy for HBP metastasis and postoperative recurrence [8]. Lobaplatin, a third-generation platinum derivative, has been proposed to be an effective intraperitoneal chemotherapeutic agent. Compared with other platinum-containing chemotherapeutic agents, lobaplatin has relatively fewer side effects causing gastrointestinal reactions, leukopenia, or thrombocytopenia [9]. Nevertheless, it can inhibit the metastasis of hepatocellular cancer, cholangiocarcinoma, and pancreatic cancer, and has been applied as the therapeutic agent for certain HBP cancer, including liver cancer, pancreatic cancer[10, 11]. However, the safeness and efficacy of lobaplatin during radical resection for HBP cancer. This study intended to investigate the safety and therapeutic efficacy of intraoperative intraperitoneal chemotherapy with lobaplatin during radical resection for HBP cancer.

Methods

Patient selection

This study was a retrospective study. Clinical data, including blood routine indicators, liver function indexes, renal function indexes, postoperative complications, survival time, and recurrence of cancer, were collected from patients with HBP cancer admitted to the Department of Hepatobiliary Surgery, Southern Hospital of Southern Medical University from June 2018 to June 2019. Surgical methods included laparoscopic surgery and open surgery. Inclusion criteria: 1)the pathological diagnosis of HBP cancer, including(hepatocellular carcinoma, cholangiocarcinoma, gallbladder carcinoma, and pancreatic carcinoma); 2]age 20–85 years; 3]preoperative imaging examination did not suggest distant metastasis and tumor thrombosis. Exclusion criteria: 1] other histories of cancer; 2]the immune system diseases, connective tissue diseases, or hematological system diseases; 3]presence of anemia, leukopenia, thrombocytopenia, or hypoproteinemia; 4]liver and kidney function is abnormal; 5]having received preoperative neoadjuvant radiotherapy or chemotherapy; 6]clinical data were incomplete. A total of 66 patients were enrolled in the study, 33 of whom underwent intraperitoneal chemotherapy with lobaplatin (study group), and 33 had no intraperitoneal chemotherapy with lobaplatin (control group). Baseline data of patients were demonstrated in Table 1.

Method of intraoperative intraperitoneal chemotherapy using lobaplatin

Patients of HBP cancer were treated with regular open or laparoscopic tumor radical resection. Lobaplatin was dissolved in normal saline to prepare a solution with 120 mg/L concentration, at the end of the operation, patients in the study group were infused with 500–1000 ml of lavage fluid with dissolved lobaplatin into the abdominal cavity. After clamping the drainage tube for 4–6 hours, the lavage fluid was drained from the abdominal cavity by opening the drainage tube.

Follow-up

The patient's followed-up time is one year. Serum tumor marker levels, abdominal ultrasound scanning and chest, and abdominal computed tomography were monitored to observe the recurrence and metastasis of cancer.

Statistical methods

A T-test or nonparametric test was used to compare the difference between the two groups. P values <0.05 (bilateral) were considered significant in all statistical analyses. Statistical Product and Service Solutions software 20.0 (IBM; Armonk, NY, USA) was used for statistical analysis.

Results

General data

A total of 66 patients were enrolled in this study, with 33 of them received intraoperative intraperitoneal infusion with lobaplatin (study group) versus 33 patients who did not receive intraoperative chemotherapy (control group). Up to December 2019, no case was lost during follow-up for assessment. The general information of patients was summarized in Table 1. Although there were statistical differences in gender and height, these parameters were with little impact on the cancer prognosis.

Table 1. General data of patients

Variables	Study group (n=33)	Control group (n=33)	T-value	P-value
Mean age (years, $\bar{X} \pm SD$)	55.21±14.01	55.24±14.33	0.009	0.993
Sex (case, n)				0.023 ^a
Male	30	21		
Female	3	12		
Hight (cm, $\bar{X} \pm SD$)	166.88±6.17	161.91 ±9.29	-2.55	0.013 ^a
Weight (kg, $\bar{X} \pm SD$)	64.39±9.13	61.92±9.71	- 1.06	0.295
BMI (kg/m ² , $\bar{X} \pm SD$)	23.16±3.29	23.66±3.48	0.596	0.533
Clinical stage (case, n)				
Liver	29	20		0.286
stage A	21	17		
stage B	7	3		
stage C	1	0		
Pancreas	4	10		0.037 ^a
I A	0	1		
II B	0	5		
III A	2	3		
III B	2	1		
Biliary tract	0	3		
II A	0	1		
II B	0	1		
T 1	0	1		

^a Indicates statistical significance, $p < 0.05$

Postoperative complications and duration of hospitalization

In the study group, there were 2 cases of inferior phrenic infection and ascites, and 1 case of postoperative leukopenia and thrombocytopenia. In the control group, one patient had an abnormal coagulation function, and one patient had gastrointestinal bleeding. These complications healed completely after appropriate medical treatment, and patients were discharged. There was no perioperative death. No statistical difference was observed in the incidence of postoperative complications or duration of hospitalization between the two groups (Table 2). These data indicated that

intraoperative intraperitoneal infusion of lobaplatin did not increase postoperative morbidity and mortality in patients with HBP cancer.

Table 2. Duration of hospitalization

Variables	Study group (n=33)	Control group (n=33)	T value	P-value
Hospitalization length (mean days, $\bar{X} \pm SD$)	16.39±8.05	14.52±6.33		0.332

Postoperative liver function, renal function, and bone marrow suppression

Liver dysfunction, renal dysfunction, and bone marrow suppression were reported as significant side effects of lobaplatin administration[12]. No patient in these two groups developed liver failure, and there was no statistical difference in levels of liver function markers between two groups, including alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin (TBIL), and albumin (ALB) at postoperative day 5 (Pod5). No statistical difference was observed in levels of renal function marker between the two groups, including creatinine (CR) and urea nitrogen (UN). No patient developed renal failure in these two groups. The levels of white blood cell (WBC) and platelet (PLT) were significantly lower in the study group compared to the control group but were still within a normal level. Moreover, no patient developed bone marrow suppression in these two groups (Table 3). These data indicated that intraoperative intraperitoneal infusion of lobaplatin did not cause postoperative liver dysfunction, renal dysfunction, or bone marrow suppression in patients with HBP cancer.

Table 3. Chemotherapy side effects (blood, liver and kidney toxicity)

Variables	Study group (n=33)	Control group (n=33)	T-value	P-value
Pod5-WBC $\times 10^9/L$	7.53±4.06	10.29±6.47		0.022 ^a
Pod5-PLT $\times 10^9/L$	161.27±75.80	238.67±143.82		0.008 ^a
Pod5-ALT U/L	93.24±93.75	84.55±168.17		0.118
Pod5-AST U/L	45.12±41.54	94.79±317.21		0.758
Pod5-ALB g/L	39.14±6.42	38.26±4.71	-0.632	0.530
Pod5-TBIL $\mu mol/L$	30.51±49.29	32.53±32.75		0.677
Pod5-CR ($\mu mol/L$)	82.75±40.67	70.05±25.94		0.344
Pod5-UREA (mmol/L)	4.78±4.28	4.53±2.58		0.888

^a Indicates statistical significance, $p < 0.05$

Postoperative recurrence and metastasis of hepatocellular cancer and pancreatic cancer

Postoperative recurrence and metastasis of hepatocellular carcinoma and pancreatic cancer were further analyzed. During a 1-year follow-up, a total of 26 patients had recurrence and metastasis of hepatocellular cancer, including 8 patients in the lobaplatin group and 18 patients in the control group. The recurrence rate of pancreatic cancer in the lobaplatin group and control was 25% and 40%, respectively ($P = 0.61$) (Table 4). The recurrence rate of hepatocellular cancer in the lobaplatin group and control was 21.14% and 60%, respectively ($P = 0.012 < 0.05$) (Table 4). However, the disease-free survival rate of a 1-year follow-up was not significantly differed between these two groups (Table 5 and Fig. 1). These data suggested that intraoperative intraperitoneal infusion of lobaplatin had the preventive potential to reduced the recurrence of HBP cancer.

Table 4. The Postoperative Recurrence and Metastasis rate

Variables	Study group (n=33)	Control group (n=33)	T-value	P-value
Liver cancer (case, n,%)	7/29(24.14%)	12/20(60%)		0.012 ^a
Pancreatic cancer (case, n,%)	1/4(25%)	4/10(40%)		0.610

^a Indicates statistical significance, $p < 0.05$

Table 5. Disease-free survival function (liver cancer)

	Card-side	df	sig
Log Rank (Mantel-Cox)	2.334	1	0.127
Breslow (Generalized Wilcoxon)	2.800	1	0.094
Tarone-Ware	2.562	1	0.109

Discussion

Radical resection is currently the most effective and preferred treatment for HBP cancer, including liver cancer, biliary cancer, and pancreatic cancer. However, postoperative recurrence and metastasis of HBP is still the leading cause of treatment failure. Currently accepted factors related to the recurrence and metastasis of HBP cancer after radical surgery include: the presence of free cancer cells in the abdominal cavity, the surgical procedures leading to shedding and implantation of cancer cells, and the injuries or dysfunction in cancer immune surveillance related to postoperative inflammation[13]. Comprehensive treatment of HBP cancer can improve the long-term clinical efficacy of HBP cancer by improving the long-term survival rate of patients and preventing tumor recurrence and metastasis. At present, intravenous systemic chemotherapy for peripheral blood vessels of patients with HBP cancer is still not efficient[14]. Intraperitoneal chemotherapy for the surgical area after HBP cancer excision might be the right choice.

Intraperitoneal chemotherapy has the following advantages: 1) Intraperitoneal chemotherapy has less stimulation to the peritoneal, gastrointestinal, and other normal abdominal contents. When chemotherapy drugs are immersed in the abdominal cavity, the drugs can effectively reach all areas of the abdominal cavity and directly target the cancer cells in the abdominal cavity, which improves the killing ability of chemotherapy drugs to the tumor cells in the abdominal cavity[15]. 2) The low intraperitoneal penetration rate of intraperitoneal chemotherapy can ensure high drug concentration[16]. 3) Intraperitoneal chemotherapy has a steady infiltration of tumor tissue, and the main reason for recurrence after hepatobiliary pancreatic cancer resection is that cancer cells invade veins to form venous cancer thrombus and microtumor thrombus, and tumor metastasis along the vein is the main route of metastasis[17, 18]. However, after the chemotherapy drugs are absorbed in the abdominal cavity, they can infuse into the liver through the portal vein and inhibit the growth of the residual tumor cells in the liver, bile, and pancreas. 4) Chemotherapy drugs can directly act on lymph nodes with tumor cell metastasis through lymphatic absorption[19]. Only a small portion of the drug infuses through the body. Thus there are fewer adverse reactions[20]. Therefore, intraperitoneal chemotherapy is currently considered as a highly specific regional chemotherapy, with less systemic adverse reactions. It has been recommended to perform postoperative early intraperitoneal chemotherapy to prevent implantation of cancer cells[21]. Our data provided evidence that intraoperative intraperitoneal chemotherapy was a safe approach with fewer side effects in patients with HBP cancer. Moreover, intraoperative intraperitoneal chemotherapy indeed decreased the recurrence or metastasis of HBP cancer after surgery.

Lobaplatin is currently the third generation of platinum drugs. It blocks the deoxyribonucleic acid (DNA) replication and transcription process by GG and AG intra-strand cross-links, thus interfering with the operation of the tumor cell cycle[22]. Its advantages include a broader anti-tumor spectrum, more potent anti-tumor activity, higher water solubility, less cross-resistance, and fewer side effects compare with other platinum-based drugs. Therefore, it is suitable for intra-abdominal chemotherapy[23]. Since chemotherapy drugs enter slowly through the “peritoneal-plasma” barrier, lobaplatin enters the body circulation within five postoperative hours, thus causing relatively less influence on the blood system and systemic toxic side reactions. When used in the veins, the most significant adverse reaction of lobaplatin is the decrease in platelet levels[24]. Our study demonstrated that lobaplatin had a relatively lighter inhibitory impact on PLT and WBC; also, it had no effects on the postoperative liver and kidney functions. Moreover, we found that intraoperative intraperitoneal chemotherapy with lobaplatin reduced the incidence of intraperitoneal implantation and metastasis of hepatocellular carcinoma, suggesting that intraoperative intraperitoneal chemotherapy using lobaplatin have a certain therapeutic significance for reducing postoperative recurrence of HBP tumor. Due to the small number of cases included in the study, further accumulation of cases is needed to obtain more data to investigate the efficacy of intraoperative intraperitoneal chemotherapy with lobaplatin for HBP cancer.

Conclusions

Intra-abdominal chemotherapy with lobaplatin after HBP carcinoma resection can effectively improve the clinical treatment effect of patients with HBP cancer, which reduces the risk of intra-abdominal

implantation metastasis and recurrence after surgery without increasing the incidence of postoperative complications.

Abbreviations

HBP: hepato-biliary-pancreatic; BMI: Body Mass Index; Pod5: postoperative day 5 ; ALT: alanine transaminase; AST: aspartate transaminase; TBIL: total bilirubin; ALB: albumin; CR: creatinine; UN: urea nitrogen; WBC: white blood cell; PLT: platelet; DNA: deoxyribonucleic acid.

Declarations

Ethics approval and consent to participate

This study was carried out following the protocols approved by the Medical Ethics Committee of Nanfang Hospital Southern Medical University (NFEC-2017-119).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Jie Zhou, Bili Zhu, and Kai Wang conceived and designed the study, and critically revised the manuscript. Gang Chen and Hao Chen analyzed the data and drafted the manuscript. Qifan Zhang, Siyun Zhang, Huanyu Li, and Qing Tan participated in study design, study implementation, and manuscript revision. All authors read and approved the final manuscript

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Not applicable.

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Figures

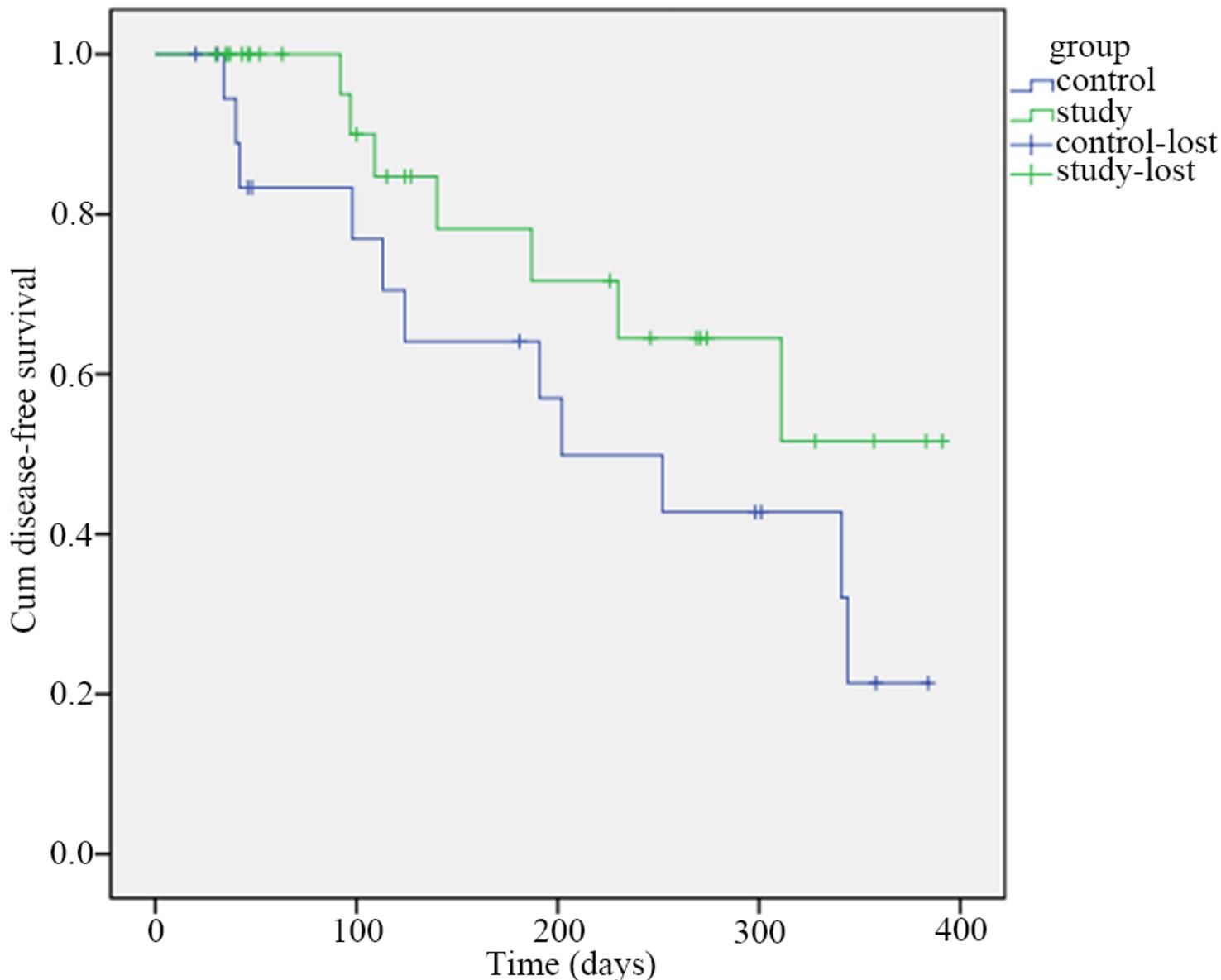


Figure 1

Disease-free survival function (liver cancer) of the study group and the control group. Study: Patients of liver cancer were treated with intraoperative intraperitoneal chemotherapy using lobaplatin Control: Patients of liver cancer were not treated with intraoperative intraperitoneal chemotherapy using lobaplatin. Study-lost: In the study group, recurrence, metastasis, and death occurred within the 1-year follow-up period. Control-lost: In the control group, recurrence, metastasis, and death occurred within the 1-year follow-up period. Kaplan-Meier curves for disease-free survival time (hepatocellular carcinoma) and cum disease-free survival (hepatocellular carcinoma) of the study group and the control group. (Disease-free survival time: 391 days for the study group vs.384 days for the control group, cum disease-free survival: 0.516 for the study group vs.0.214 for the control group.)