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Retrospective Study

Efficacy of transcatheter arterial chemoembolization using pirarubicin-loaded microspheres combined with lobaplatin for primary liver cancer

Abstract

BACKGROUND

Drug-eluting beads show a good safety and promising efficacy when used as part of a transarterial chemoembolization regimen for primary liver cancer. However, data on the clinical efficacy and safety of pirarubicin-loaded beads combined with lobaplatin are lacking in China.

AIM

To evaluate the efficacy and safety of transcatheter arterial chemoembolization (TACE) using pirarubicin-loaded beads combined with lobaplatin for primary liver cancer.

METHODS

Between January 2019 and March 2020, 60 patients with primary liver cancer were selected at Hebei North University Affiliated First Hospital. According to different treatment methods, the participants were categorized into two groups with 30 patients treated with pirarubicin loaded microspheres combined with lobaplatin included in an observation group and 30 patients treated with pirarubicin emulsion with lipiodol combined with lobaplatin were included in a control group. The progression free survival (PFS), overall survival, clinical response rate, disease control rate, liver and kidney function and adverse reactions were compared between the two groups.

RESULTS

The PFS was 14 mo in the observation group, which was significantly higher than 9 mo of the control group ($P < 0.05$). The 6-month, 12-month and 18-month survival rates were 93.33% (28/30), 66.67% (20/30) and 23.33% (7/30), respectively in the observation group, which were significantly higher than 83.33% (25/30), 50.00% (15/30) and 13.33% (4/30), respectively of the control group (all $P < 0.05$). The clinical efficacy rate and disease control rate were 73.33% and 93.33%, respectively in the observation group, which were significantly higher than those of the control group (53.55% and 80.00%, respectively, all $P < 0.05$). There was no significant difference in alpha-fetoprotein (AFP) between the two groups before the treatment ($P > 0.05$). After the treatment, AFP was 289.06 ± 76.21 ng/mL in the observation group and 365.01 ± 73.11 ng/mL in the control group, which were low in both groups compared with those before the treatment (all $P < 0.05$). The incidence of nausea and vomiting was significantly lower in the observation group than in the control group ($P < 0.05$). There was no significant difference for the adverse reactions of pain and fever between the two groups ($P < 0.05$).

CONCLUSION

The combination of pirarubicin-loads beads and lobaplatin can improve treatment efficacy resulting in mild liver function damage and postoperative complications in patients with primary liver cancer. It can be used in clinical practice.

Key Words: Pirarubicin; Drug-loaded microspheres; Lobaplatin; Transcatheter arterial chemoembolization; Primary liver cancer

INTRODUCTION

Primary liver cancer is one of the malignant diseases of digestive system with high morbidity and mortality[1,2]. The number of deaths caused by primary liver cancer in China per annum is half of deaths in the world. Currently, the main therapies for primary liver cancer include liver transplantation, surgical resection, local ablation therapy, transcatheter arterial chemoembolization (TACE) and targeted therapy[3,4]. The onset of this disease is insidious and it develops very fast. When primary liver cancer is confirmed in a patient, generally it means a high degree of malignancy and the patient has lost the best opportunity of surgical resection[5]. Encouragingly, TACE is increasingly used in the clinical treatment of primary liver cancer with the advancement in the treatment approaches[6]. Lipiodol as a carrier for chemotherapy agents can selectively deliver agents into micro-vessels in liver tumor tissues *via* the hepatic artery, which improves the treatment efficacy for liver cancer[7]. Liposoluble chemotherapy agents dissolved in lipiodol can stay longer in liver tumor, which may strengthen the anti-tumor efficacy of chemotherapy agents[8]. Drug-eluting microspheres as a new embolic agent for peripheral vessels in tumor, can enhance embolization efficacy and is independent of the impact that embolic materials may be washed away by blood flow as well as that of tissue degradation[9]. Studies showed that intervention therapies with lobaplatin pirarubicin revealed obvious efficacy for primary liver cancer with mild adverse reactions and prolonged survival[10,11]. The present study aims to discuss the efficacy of TACE with pirarubicin-loaded microspheres combined with lobaplatin for primary liver cancer and progress-free survival (PFS), overall survival, clinical response rate, disease control rate, liver and kidney function and adverse reactions.

MATERIALS AND METHODS

Participants

Sixty patients with primary liver cancer were selected at Hebei North University Affiliated First Hospital between January 2019 and March 2020. They were categorized into two groups based on the treatment approaches. Thirty patients receiving pirarubicin loaded microspheres combined with lobaplatin included in an observation

group and 30 patients receiving pirarubicin emulsion with lipiodol combined with lobaplatin were included in a control group. The current study was approved by hospital ethics committee and all included patients signed the informed consent form for the academic research.

Inclusion criteria for this study were as the follows: (1) patients who were pathologically diagnosed with primary liver cancer after a biopsy; (2) patients with class of liver function A to B; (3) patients whose alpha-fetoprotein (AFP) was above 50 ng/mL; (4) patients without metastasis or portal vein thrombosis; and (5) patients whose tumor volume was less than 60% of liver volume. Exception criteria for this study included: (1) patients with severe heart, liver, and kidney dysfunction; (2) patients with other types of cancer; (3) patients with iodine allergy; and (4) patients who had arteriovenous shunt. Of 30 patients in the observation group, 24 were male and 6 were female aged 34 to 66 (52.13 ± 13.12) years. In terms of Child-Pugh classification for liver function, 25 were class A patients and 5 were class B patients. For complications, 18 patients had hepatitis B virus and 17 patients had hepatocirrhosis. Of 30 patients in the control group, 25 were male and 5 were female aged 33 to 65 (50.36 ± 11.09) years. Regarding Child-Pugh classification for liver function, 26 were class A patients and 4 were class B patients. Concerning complications, 19 patients had hepatitis B virus and 16 patients had hepatocirrhosis. The general information was comparable between the two groups ($P > 0.05$).

Protocols

For the observation group, a 5-F tube introducer was inserted following femoral artery puncture. Routine radiography of celiac arteries and superior mesenteric arteries including left gastric arteries, bilateral phrenic arteries, right suprarenal arteries, internal thoracic arteries, and intercostal arteries was performed to determine feeding arteries and whether hepatic arterioportal fistulas or hepatic arterial venous fistulas existed. Then a 2.2-F microcatheter was inserted into feeding artery branches for chemoembolization. First, 50 to 150 mg of lobaplatin (H20080359; Hainan Changan

International Parmaceutical Co., Ltd., China) was perfused based on patients' disease severity. Afterwards, 5 to 40 mL of pirarubicin loaded microspheres (H10930105; Shenzhen Main Luck Parmaceuticals Inc., China) was injected fluoroscopically at a slow pace. Patients were closely monitored until blood flow interruption occurred within the blood vessels on radiography and until the staining disappeared. The operation for the control group is similar with that of the observation group. In the same way, 50 to 150 mg of lobaplatin was perfused based on patients' condition. Then pirarubicin emulsion with lipiodol combined with lobaplatin was injected. Also, they were closely monitored until blood flow was interrupted on radiography and until the staining disappeared. Patients in both groups were followed-up for 18 mo after the operation.

Measures

PFS was estimated after a follow-up of 18 mo. Overall survival at 6, 12 and 18 mo was compared between the two groups. Short-term efficacy was compared between the two groups based on [8] Evaluation Criteria in Solid Tumors. Complete remission (CR) was defined as all contrast enhancement of targeted lesions in arterial phase disappeared. Partial remission (PR) was defined as the total sum of diameter for contrast enhancement of targeted lesions in arterial phase reduced ≥ 30%. Stable disease (SD) was defined as a reduction in tumor enhancement intensity in the arterial phase on contrast-enhanced computed tomography but PR or progressive disease (PD) was not observed. PD was defined as the total sum of diameter for contrast enhancement of targeted lesions in arterial phase increased ≥ 20% or new lesions were observed. Clinical efficacy = CR + PR. Disease control rate = CR + PR + SD. AFP was used to analyze hepatic and renal function. High AFP is associated with great hepatic injury. In addition, adverse reactions were compared between the two groups.

Statistical analysis

SPSS22.0 software was used for data processing. Student t test was used for quantitative variables which was reported with mean ± SD. χ^2 test was used for qualitative variables and was presented as (%). $P < 0.05$ represented there was a significant difference.

RESULTS

PFS was 14 mo in the observation group which was higher than 9 mo of the control group ($P < 0.05$). The 6-, 12- and 18-mo survival was 93.33% (28/30), 67.77% (20/30) and 23.33% (7/30), respectively, which was higher than 83.33% (25/30), 50.00% (15/30) and 13.33% (4/30), respectively of the control group (all $P < 0.05$).

In terms of treatment efficacy, the clinical efficacy and disease control rate was 73.33% and 93.33%, respectively, which was higher than 53.55% and 80.00%, respectively in the control group (all $P < 0.05$, Table 1).

For AFP, there was no significant difference in AFP between the two groups before the treatment ($P > 0.05$). After the treatment, AFP was 289.06 ± 76.21 ng/mL in the observation group and 365.01 ± 73.11 ng/mL in the control group. AFP was low after the treatment compared with those before the treatment and it was significantly lower in the observation group than in the control group (all $P < 0.05$, Table 2).

After comparing adverse reactions after the treatment, it founded primary adverse reactions included nausea and vomiting, pain, and fever, and most of them were mild to moderate. The incidence of nausea and vomiting was significantly lower in the observation group than in the control group (all $P < 0.05$, Table 3). However, there was no significant difference in the incidence of pain and fever between the two groups ($P > 0.05$).

DISCUSSION

Currently, imaging and biopsy after resection were generally used for the diagnosis of primary liver cancer. However, most patients with liver cancer developed advanced stages when they were diagnosed, which causes the disease hard to treat and leads to high mortality[12,13]. The optimal treatment for liver cancer is surgical resection, which

can thoroughly remove the primary lesions and the recurrence rate is low. However, this therapy only applies to early-stage primary liver cancer patients with Child-Pugh class A or B and without metastasis[14,15]. For patients who were considered ineligible for surgery, the well-accepted therapy of transcatheter arterial chemoembolization is used, which can effectively inhibit the development of primary liver cancer by blocking the blood flow to a tumor in the liver and cutting off liver tumor's nutrient supply[16,17]. Clinical studies showed that arterial embolization using micro catheter can directly embolize blood supply to tumors and cut off nutrient supply for tumor growth[18]. Meanwhile, pirarubicin loaded microspheres combined with lobaplatin contribute to a thorough embolism, which may inactivate tumor cells and tissues to some extent to inhibit tumor growth and realize tumor atrophy and necrosis[19,20]. Moreover, hepatic artery embolization using lipiodol-based emulsion alone can easily lead to hepatic necrosis or biliary duct necrosis, which may increase the burden of liver function[21,22]. Favorably, microsphere embolism can effectively reduce tumor feeding arteries, embolize tumors, reduce establishment of collateral circulation for incomplete tumor necrosis and cut off nutrient supply for tumor growth[23].

Microspheres loaded with pirarubicin combined with lobaplatin can facilitate concentration of chemotherapeutic agents to a high level for a prolonged period in local tumors. In this way, concentration of chemotherapeutic agents in the systemic circulation was reduced thus mitigating adverse effects of these agents in other organ systems and to lower the incidence of complications. The present study manifested that pirarubicin loaded microspheres combined with lobaplatin can extend survival in patients undergoing TACE. The 6-, 12- and 18-month survival was higher in patients receiving pirarubicin loaded microspheres combined with lobaplatin than those receiving pirarubicin emulsion with lipiodol combined with lobaplatin for TACE. Meanwhile, the clinical treatment efficacy and disease control rate was high in patients receiving pirarubicin loaded microspheres combined with lobaplatin compared with those receiving pirarubicin emulsion with lipiodol combined with lobaplatin. The effect of pirarubicin loaded microspheres combined with lobaplatin was relatively small and

the adverse reactions were mild after treatment. Further researches are needed to confirm these findings.

CONCLUSION

The efficacy is good and adverse reactions are mild in patients with primary liver cancer undergoing TACE using pirarubicin loaded microspheres combined with lobaplatin. Large scale studies with long follow-up periods are needed to further investigate these results.

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Table 1 Efficacy of the two treatment approaches, *n* (%)

Groups	CR	PR	SD	PD	Clinical efficacy (%)	Disease control rate (%)
Observation group (*n* = 30)	7 (23.33)	15 (50.00)	6 (20.00)	2 (6.67)	73.33	93.33
Control group (*n* = 30)	5 (16.67)	11 (36.67)	8 (26.67)	6 (20.00)	53.33	80.00
χ^2 value					15.521	5.660
P value					0.001	0.041

Clinical efficacy = Complete remission + partial remission; Disease control rate = Complete remission + partial remission + stable disease. CR: Complete remission; PR: Partial remission; SD: Stable disease.

Table 2 Comparison of alpha-fetoprotein between the two groups before and after the treatment (mean ± SD, ng/mL)

Groups	Before the treatment	After the treatment
Observation group (*n* = 30)	621.07 ± 154.76	289.06 ± 76.21
Control group (*n* = 30)	609.76 ± 145.69	365.01 ± 73.11
t value	1.024	6.843
P value	0.237	0.034

Table 3 Incidence of adverse reactions in the two groups after the treatment, *n* (%)

Groups	Nausea and vomiting	Pain	Fever
Observation group (*n* = 30)	9 (30.00)	21 (70.00)	11 (36.67)
Control group (*n* = 30)	19 (63.33)	22 (73.33)	12 (40.00)
χ^2 value	6.421	0.245	0.312
P value	0.035	0.543	0.564

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