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

Chao Zhang, Yu-Hui Dai, Shu-Feng Lian, Liang Liu, Ting Zhao, Jun-Ye Wen

BACKGROUND

Drug-eluting beads show good safety and promising efficacy when used as part of a transcatheter 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 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, overall survival, clinical response rate, disease control rate, liver and kidney function and adverse reactions were compared between the two groups.
RESULTS
The progression-free survival was 14 mo in the observation group, which was significantly higher than 9 mo of the control group ($P < 0.05$). The 6-mo, 12-mo and 18-mo 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 between the two groups before the treatment ($P > 0.05$). After the treatment, alpha-fetoprotein was $289.06 \pm 76.21$ ng/mL in the observation group and $365.01 \pm 73.11$ 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-loaded 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

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Core Tip: Drug-eluting beads, a relatively novel drug delivery embolization system, show advantages over the conventional lipiodol embolization in the most used interventional therapy of transcatheter arterial chemoembolization for unresectable hepatic carcinoma. This study investigated the efficacy and safety of transcatheter arterial chemoembolization using pirarubicin-loaded beads combined with lobaplatin for primary liver cancer in comparison with conventional transcatheter arterial chemoembolization. The results revealed this combination therapy can increase treatment efficacy and improve hepatic function in patients with primary liver cancer.

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INTRODUCTION
Primary liver cancer is one of the malignant diseases of the 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 the 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[3]. 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 microvessels in liver tumor tissues via the hepatic artery, which improves the treatment efficacy for liver cancer[7]. Liposoluble chemotherapy agents dissolved in lipiodol remain in the liver tumor longer, which may strengthen the anti-tumor efficacy of chemotherapy agents[8].

Drug-eluting microspheres, as a new embolic agent for peripheral vessels in tumors, can enhance embolization efficacy and is independent of the impact of embolic materials being 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 aimed to discuss the efficacy of TACE with pi-
Zhang C et al. TACE in primary liver cancer

rubicin-loaded microspheres combined with lobaplatin for primary liver cancer and determine progression-free survival, 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 were included in an observation group, and 30 patients receiving pirarubicin emulsion with lipiodol combined with lobaplatin were included in the control group. The current study was approved by the hospital ethics committee, and all included patients signed the informed consent form for the academic research.

Inclusion criteria for this study were as 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 the liver volume. Exclusion 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 an arteriovenous shunt.

Of the 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 arteriportal fistulas or hepatic arterial venous fistulas existed. Then a 2.2-F microcatheter was inserted into the feeding artery branches for chemoembolization. First, 50 to 150 mg of lobaplatin (H20080359; Hainan Changan International Pharmaceutical Co., Ltd., China) was perfused based on each patient’s disease severity. Afterwards, 5 to 40 mL of pirarubicin-loaded microspheres (H10930105; Shenzhen Main Luck Pharmaceuticals Inc., China) were 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 was similar to the observation group. In the same way, 50 to 150 mg of lobaplatin was perfused based on each patient’s 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
Progression-free survival was estimated after a follow-up of 18 mo. Overall survival at 6 mo, 12 mo and 18 mo was compared between the two groups. Short-term efficacy was compared between the two groups based on Evaluation Criteria in Solid Tumors. Complete remission was defined as all contrast enhancement of targeted lesions in the arterial phase had disappeared. Partial remission (PR) was defined as the total sum of the diameter for contrast enhancement of targeted lesions in the arterial phase reduced ≥ 30%. Stable disease was defined as a reduction in tumor enhancement intensity in the arterial phase had disappeared. Partial remission (PR) was defined as the total sum of the diameter for contrast enhancement of targeted lesions in the arterial phase increased by ≥ 20% or new lesions were observed. Clinical efficacy = complete remission + PR. Disease control rate = complete remission + PR + stable disease. AFP was used to analyze hepatic and renal function. Higher AFP is associated with greater hepatic injury. In addition, adverse reactions were compared between the two groups.

Statistical analysis
SPSS22.0 software was used for data processing. Student’s \( t \) test was used for quantitative variables, which was reported with mean ± SD. \( \chi^2 \) test was used for qualitative variables and was presented as (%). \( P < 0.05 \) represented a significant difference.
RESULTS

Progression-free survival was 14 mo in the observation group, which was higher than 9 mo of the control group ($P < 0.05$). The 6-mo, 12-mo 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).

There was no significant difference in AFP between the two groups before the treatment ($P > 0.05$). After the treatment, AFP was $289.06 \pm 76.21$ ng/mL in the observation group and $365.01 \pm 73.11$ 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, the primary adverse reactions included nausea and vomiting, pain and fever. 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 are generally used for the diagnosis of primary liver cancer. However, most patients with liver cancer develop advanced stages before they are diagnosed, which causes the disease to be 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 TACE 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 the liver tumor’s nutrient supply\[16,17\]. Clinical studies showed that arterial embolization using a microcatheter 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 and to some extent inhibit tumor growth causing 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 concentrations of chemotherapeutic agents to a high level for a prolonged period in local tumors. In this way, concentrations 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-mo, 12-mo 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 studies 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.
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 |
| χ² 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; PD: progressive 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)    |
| χ² value                | 6.421                | 0.245         | 0.312         |
| P value                  | 0.035                | 0.543         | 0.564         |

ARTICLE HIGHLIGHTS

Research background
Transcatheter arterial chemoembolization (TACE) using microspheres as the drug carrier and embolization agent shows good efficacy and safety for the treatment of liver cancer compared with conventional chemotherapy.

Research motivation
Data on the clinical efficacy of TACE using pirarubicin-loaded microspheres combined with lobaplatin is rare in China.

Research objectives
This study evaluated the effectiveness and safety of TACE using pirarubicin-loaded microspheres combined with lobaplatin for treatment of primary liver cancer.

Research methods
In this observational study, patients with primary liver cancer undergoing TACE were recruited at Hebei North University Affiliated First Hospital. Patients were categorized into an observation group and a control group based on different types of embolic agents. The observation group received pirarubicin-loaded microspheres combined with lobaplatin, and the control group received conventional pirarubicin emulsion with lipiodol combined with lobaplatin. The primary outcomes included progression-free survival, overall survival, clinical response rate, disease control rate, liver and kidney function, and adverse reactions.

Research results
In general, the treatment efficacy was better in the observation group than in the control group. Progression-free survival was higher in the observation group than in the control group. After the
treatment, alpha-fetoprotein, which represents hepatic function, was lower in the observation group than in the control group. For the primary adverse reactions, the incidence of nausea and vomiting was lower in the observation group than in the control group. However, there was no significant difference in the incidence of pain and fever between the two groups.

**Research conclusions**

Pirarubicin-loaded microspheres combined with lobaplatin can extend survival and improve hepatic function in patients undergoing TACE compared with those receiving pirarubicin emulsion with lipiodol combined with lobaplatin.

**Research perspectives**

Further research is needed to better investigate the long-term efficacy and safety of cancer microsphere intervention in patients with primary liver cancer.

**FOOTNOTES**

**Author contributions:** Zhang C, Dai YH, Lian SF, Liu L, Zhao T and Wen JY designed the research study; Zhang C and Dai YH performed the research; Zhang C, Dai YH, Lian SF, Liu L, Zhao T and Wen JY analyzed the data and wrote the manuscript; All authors have read and approved the final manuscript.

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