In Vivo Evaluation of Irinotecan-Loaded QuadraSphere Microspheres for Use in Chemoembolization of VX2 Liver Tumors

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ABSTRACT

Purpose: To investigate the pharmacokinetics and chemoembolization efficacy of irinotecan-loaded QuadraSphere microspheres (QSMs) in a rabbit VX2 liver tumor model.

Materials and Methods: Fourteen rabbits with VX2 liver tumors were divided into two groups. In the irinotecan-loaded QSM group (n = 7), 3 mg of QSMs (30–60 μm) containing 12 mg of irinotecan (0.6 mL; 20 mg/mL) were injected into the left hepatic artery. In the control group (hepatic arterial infusion [HAI] and QSMs; n = 7), 3 mg of QSMs suspended in ioxaglic acid were injected following a bolus injection of 0.6 mL of irinotecan solution (20 mg/mL). Sequential irinotecan, SN-38, and SN-38G concentration changes were measured in plasma within 24 hours and at 1 week and in tissues at 1 week. The VX2 tumor growth rates at 1 and 2 weeks were calculated from computed tomographic images.

Results: All rabbits underwent successful embolization. Plasma irinotecan, SN-38, and SN-38G concentrations in the irinotecan-loaded QSM group showed significantly sustained release compared with the control group ($P = .01$). Compared with the control group, the irinotecan-loaded QSM group had significantly higher irinotecan concentration in liver tumors ($P = .03$) and a tendency toward higher SN-38 concentration in liver tumors ($P = .29$). The SN-38G tissue concentrations were below the limits of quantification. The tumor growth rate was significantly lower and the tumor necrosis rate significantly higher in the irinotecan-loaded QSM group ($P = .02$ and $P = .01$, respectively).

Conclusion: Chemoembolization via irinotecan-loaded QSMs more effectively suppresses tumor growth than chemoembolization with unloaded QSMs after HAI. A clinical feasibility study is warranted.

ABBREVIATIONS

AUC = area under the concentration–time curve, CRC = colorectal carcinoma, HAI = hepatic arterial infusion, QSM = QuadraSphere microsphere

The survival of patients with metastases of colorectal carcinoma (CRC) has been improved by recent developments in chemotherapy (1–4), whereas approximately 92% in patients treated with irinotecan-based second-line chemotherapy will experience disease progression, with a median progression-free survival interval of 3.8 months (5). Recently, clinical results of transarterial chemoembolization with the use of irinotecan-loaded embolic agents for liver metastases from CRC have been reported (6–11). Theoretically, transarterial chemoembolization with drug-eluting embolic agents is characterized by ischemia and local drug accumulation with limited systemic exposure. There are three types of embolic agents capable of loading irinotecan, QuadraSphere microspheres (QSMs; Merit Medical, South

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Jordan, Utah), DC Bead (Biocompatibles, Farnham, United Kingdom), and Embozene TANDEM Microspheres (CeloNova BioSiences, San Antonio, Texas).

Although an in vitro study showed QSMs released most of the loaded irinotecan in a few minutes (12), to our knowledge, there have been no in vivo evaluations regarding the pharmacokinetic advantages of irinotecan-loaded QSMs. The purpose of the present study was to investigate the local and systemic pharmacokinetics and the efficacy of irinotecan-loaded QSMs in a rabbit VX2 liver tumor model. In addition, we compared these results with those in a control group treated with hepatic arterial infusion (HAI) of irinotecan plus QSMs.

MATERIALS AND METHODS

Animal Model

The study protocol was approved by the animal experimentation committee, and the experiments were performed in accordance with the animal care guidelines of our institution. Fourteen female New Zealand White rabbits (mean weight, 3.05 kg; range, 2.86–3.20 kg; Kitayama Labes, Nagano, Japan) were anesthetized by intramuscular injection of 0.2 mg/kg medetomidine hydrochloride (Dorbene; Kyoritsuseiyaku, Tokyo, Japan), 10 mg/kg ketamine hydrochloride (Ketalar; Diichi Sankyo, Tokyo, Japan), and 0.5 mg/kg butorphanol tartrate (Vetorphale; Meiji Seika Pharma, Tokyo, Japan). A small midline incision was made, and the left liver lobe was exposed. The VX2 tumors were cut into 1-mm^3 cubes, and three pieces were inserted into one site in each left liver lobe. The abdominal wall was sutured in two layers. The rabbits were studied 2 weeks after tumor implantation.

Preparation of Chemotherapeutic and Embolic Agents

Irinotecan solution (20 mg/mL; Nihon Kayaku, Tokyo, Japan) was loaded into QSMs 2 hours before injection. The size of the QSMs was 30–60 μm in the dry state, and the microsphere diameter was increased by a factor of approximately 2.6 times (78–156 μm) by the loading of irinotecan solution (13). For the control group, 30–60-μm QSMs were swollen to two times their original size in 320 mgI/mL ioxaglic acid (Hexabrix; Terumo, Tokyo, Japan) (14,15), and the diameter of QSMs was similar in both groups.

Tumor Treatment Procedure

The femoral artery was surgically exposed, and a 4-F sheath (SuperSheath; Medikit, Tokyo, Japan) was inserted. Under fluoroscopic guidance, a 4-F catheter (Selecon PA catheter, Berenstein type; Terumo Clinical Supply, Gifu, Japan) was inserted into the celiac axis, and a 1.8-F microcatheter (Pixie; Tokai Medical Products, Aichi, Japan) was advanced coaxially into the left hepatic artery. We referred to the arterial anatomy described by Seo et al (16). Chemoembolization and intra-arterial chemoinfusion/embolization were performed in approximately 6 minutes. Irinotecan-loaded QSMs were invisible under radiographic fluoroscopy because they were flushed with distilled water to prevent elution of irinotecan from irinotecan-loaded QSMs in a syringe and a microcatheter during injection. Therefore, chemoembolization was performed without fluoroscopic guidance (13).

Study Design and Treatment Groups

In each rabbit, 3 mg of QSMs and 12 mg of irinotecan in solution were injected into the left hepatic artery. Fourteen rabbits were randomly divided into two groups. Rabbits in the irinotecan-loaded QSM group ($n = 7$), received 3 mg of QSMs containing 12 mg of irinotecan in solution, and rabbits in the control group (ie, HAI and QSMs; $n = 7$), received 3 mg of QSMs (30–60 μm in diameter) suspended in 0.6 mL of ioxaglic acid (320 mgI/mL) immediately after bolus injection of an equivalent amount of irinotecan solution. Twelve rabbits were euthanized at 7 days, and the following five variables were determined: (i) irinotecan, SN-38 (active metabolite of irinotecan), and SN-38G (inactive metabolite of SN-38) concentrations in plasma; (ii) irinotecan, SN-38, and SN-38G concentration in local tissues; (iii) growth rate of the VX2 tumor; (iv) serum chemistry; and (v) histopathologic variables. One rabbit in each group ($n = 2$) was euthanized at 14 days, and the growth rates of the VX2 tumor were calculated.

Pharmacokinetic Analysis

Blood samples (3 mL) were collected at 5, 10, 30, and 60 minutes and at 1 and 7 days. Another 1-mL blood sample was collected just before the procedures and at 1 and 7 days to determine the serum levels of aspartate aminotransferase, alanine aminotransferase, albumin, total bilirubin, lactase dehydrogenase, alkaline phosphatase, and γ-glutamyl transpeptidase.

The entire liver was excised and carefully removed. Samples (approximately 5-mm^3 cubes) of liver tumors, liver parenchyma adjacent to the tumor, and liver parenchyma at least 1 cm apart from the tumor were obtained for determination of tissue irinotecan, SN-38, and SN-38G concentration. The plasma or tissue concentration was determined by using high-performance liquid chromatography (Alliance HPLC; Nihon Waters, Tokyo, Japan).

For pathologic evaluation, the liver samples (5-mm^3 cubes) were embedded in paraffin. The paraffin blocks were cut at nominal 4-μm intervals and stained with hematoxylin and eosin. The tumor necrosis rate was estimated by visual inspection by using a whole-slide imaging device (NanoZoomer 2.0-HT; Hamamatsu Photonics, Shizuoka, Japan).