Intra-arterial Iodine 131–Labeled Lipiodol as Adjuvant Therapy After Curative Liver Resection for Hepatocellular Carcinoma

A Phase 2 Clinical Study

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Hypothesis: Intra-arterial lipiodol labeled with iodine 131 (131I-lipiodol) can be safely used as adjuvant therapy following curative liver resection for hepatocellular carcinoma (HCC).

Design: Phase 2 pilot study.

Setting: Large teaching hospital.

Patients: Twenty-eight patients (24 men and 4 women; median age, 61.5 years; range, 33-75 years) were treated from January 1991 to June 1997. The liver was cirrhotic in 7 cases and noncirrhotic in 21 cases. An equal number of 14 patients underwent a major and a minor resection, all with clear margins. Median diameter of solitary tumors or the larger tumor when multiple tumors occurred was 5.5 cm (range, 2.5-29 cm). Tumor encapsulation was present in 12 cases and absent in 16 cases. After informed consent, patients who had no evidence of residual or recurrent tumor on computed tomographic (CT) scan and no sign of liver failure 2 to 3 months after curative resection for HCC were included in the trial. Complete follow-up was obtained (median, 51 months; range, 5-93 months).

Interventions: A 1110-MBq dose of 131I-lipiodol was administered into the hepatic artery using the Seldinger technique. Patients were kept in a radio-protected room for 5 days. Postinjection radioactive whole scintiscan was performed at 5 days and an abdominal CT scan at 1 month after the injection. A second injection was performed in 16 patients 2 years later using the same protocol.

Main Outcome Measure: Procedure safety.

Results: All patients experienced transient fever during the first 12 hours following injection. There were no noted adverse clinical effects or significant alteration in hepatic function due to the procedure or at immediate and late follow-up. The radioactive scan demonstrated an intense liver uptake, which was homogeneous in 19 cases and heterogeneous in 9. Mild detectable thyroid and lung uptake occurred in 50% of cases. No lipiodol liver fixation was observed on the 1-month CT scan. At the time of follow-up, 6 patients had died and 12 had developed recurrences, with 5 of the 6 deaths belonging to the recurrent group. Sixteen patients remained disease free. The median time to detected recurrence was 28 months (range, 12-62 months). Overall survival rates were 86% at 3 years and 65% at 5 years.

Conclusions: This pilot study failed to demonstrate any clinically significant adverse effect of adjuvant therapy by intra-arterial 131I-lipiodol after curative liver resection for HCC. Long-term survival compares favorably with those undergoing only surgery and suggests a benefit in lowering tumor recurrence. A randomized, multicenter, prospective trial comparing patients treated with intra-arterial 131I-lipiodol with a nontreated control group seems appropriate.

Arch Surg. 2000;135:1298-1300

LONG-TERM RESULTS following hepatectomy for hepatocellular carcinoma (HCC) are not yet satisfactory,1 with 80% recurrence at 3 years even with clear resection margins. When technically possible, the 5-year survival rate is usually less than 30%.2 The principal cause of death following hepatectomy is intrahepatic recurrences, usually during the first years after surgery. Prevention and treatment of intrahepatic recurrence after hepatic resection have been considered to be the most important factors required to obtain better surgical results.3 Lipiodol ultrafluid (Lipiodol Laboratoire, Guerbert, France) is an ethyl ester of the fatty acid derived from a poppy seed oil containing 38% iodine by weight. Used commercially as a lymphangiogram dye, this agent has been reported to concentrate in the tumoral tissue of patients with HCC after injection into the hepatic artery. Although the exact mechanism of this long-term deposition remains unclear, intra-arterial lipiodol injection and computed tomographic (CT) scan are currently used in clinical practice for detection...
PATIENTS AND METHODS

The protocol was approved by the Committee for Patients’ Protection in accordance with the Huriet Law, which controls all clinical investigations in France. Written informed consent was obtained for every patient. Patients who had undergone curative resection for HCC, defined by macroscopically complete removal of the tumor tissue, and who recovered following their operation were selected for inclusion in the study. Patients were readmitted to the hospital 2 to 3 months after liver resection for evaluation before inclusion. Abdominal ultrasonography, CT scan, and chest x-ray examination were performed. Liver function and α-fetoprotein levels were assessed. Patients were included in the trial if they had no evidence of residual recurrent disease and no sign of liver failure. Angiography had been performed before the procedure to assess the anatomy and exclude a major shunt. The femoral artery was punctured and the hepatic artery catheterized using a Seldinger technique to perform selective angiography. A single dose of 1110 MBq of 131I-lipiodol emulsified with sodium and meglumine ioxaglate (Hexabrix 320; Laboratoires Guerbet, Aulnay-sous-bois, France) by an automat was injected into the hepatic artery. The emulsion was composed of 70% of micelles with a diameter of less than 4 µm and a constant granulometric composition for 72 hours. In the case of a double hepatic arterial inflow, both arteries were catheterized and injected with a half dose each. Liver function was assessed at day 5 after injection and at 1, 3, and 6 months. Patients were transferred to the Unit of Nuclear Medicine and remained in a radio-protected room during the 5 days following the injection. A whole-body scintigraphy was performed 3 days later for the whole series, and the radioactive uptake by the liver, lungs, and thyroid was assessed. The first 10 patients also underwent repeated whole-body scanning at days 2, 5, 8, and 10 to study the biodistribution of 131I-lipiodol. All patients were submitted to a systematic follow-up. The CT scans were performed 1 month after the procedure and were repeated annually. Ultrasound examination and liver function tests were performed and α-fetoprotein levels were measured every 6 months to detect recurrence. The protocol included performance of a second 131I-lipiodol injection 2 years postoperatively, identical to the original protocol, in the disease-free patients. Patients with recurrence were treated according to their general status and with regard to both the location and extension of the tumor, either by additional resection, chemoembolization, percutaneous alcohol injection of the tumor, or palliative care.

of satellite or multicentric nodules in patients with limited-stage HCC. Lipiodol mixed with anticancer agents has also been administered via the hepatic artery for treatment of unresectable HCC. Various procedures are derived from this technique, such as lipiodolization, chemolipiodolization, transcatheter oily chemoembolization, and embolization with gelatin sponge or gel foam particles at the end of the procedure, with most gaining wide clinical application. Lipiodol labeled with iodine 131 (131I-lipiodol) injected into the hepatic artery has been investigated for clinical applications after its biodistribution had been tested for safety and utility. It has been considered to be an effective treatment for patients with unresectable HCC. Our hypothesis was that it may also eradicate the residual microscopic disease or kill cells with high-grade dysplasia in the liver remnant after liver resection. The aims of the present study (a phase 2 pilot trial) were to determine whether adjuvant intra-arterial 131I-lipiodol could be performed safely after liver resection for HCC and to obtain information about the local recurrence rate, disease-free survival, and overall survival before embarking on a phase 3 randomized trial.

RESULTS

PATIENTS

From 1991 to 1997, 28 patients underwent a liver resection for HCC and were treated 2 to 6 months postoperatively by intra-arterial injection of 131I-lipiodol. There were 24 male patients and 4 female patients (median age, 61.5 years; range, 33-75 years). Hepatocellular carcinoma had developed in cirrhotic livers in 7 patients and in noncirrhotic livers in 21 patients. Twenty patients had solitary tumor, and 8 patients had multiple tumor nodules (not more than 4). Median maximum size of the tumor was 5.5 cm (range, 2.5-29 cm). The tumor nodules were greater than 5 cm in 17 patients. Vascular invasion into a portal branch was present in 2 cases. The median period of follow-up was 51 months (range, 5-93 months). At the time of follow-up, 6 patients had died, 5 with recurrent disease. There were a total of 12 patients who had developed recurrent disease at a median period of 28 months (range, 12-62 months).

LIVER RESECTION

The liver resection was a segmentectomy or bisegmentectomy in 10 cases, a left hepatectomy in 9 cases, and a right hepatectomy in 9 cases (with extension of the resection to segment 4 in 2 patients). Margins were histologically clear in all cases, and no evidence of extrahepatic spread was detected.

131I-LIPIODOL INJECTION

Median interval between liver resection and 131I-lipiodol injection was 3 months (range, 1-10 months). 131I-lipiodol was successfully injected in every patient under fluoroscopic control. Catheterization of the hepatic artery via the femoral route failed in only 1 patient because of the tortuosity of the artery. The patient underwent a second successful procedure via the axillary route. 131I-lipiodol biodistribution was calculated for the first 10 patients with an effective isotope half-life of 63 hours. Uptake was observed to be mild (<8% observed in the lung on day 1 and <5% in the thyroid) in all patients. The percentage of liver uptake at postinjection day 1 was...
74%±14.4% of the injected activity. Fourteen patients who were alive and disease free 2 years postoperatively underwent a second 131I-lipiodol injection according to the same protocol.

FOLLOW-UP

At the time of follow-up, 16 patients remained disease free, with 1 death occurring in this group unrelated to HCC. An additional 5 patients had died from recurrent disease (2 with recurrence in the liver), and the remaining 7 patients had recurrent disease that, depending on the clinical situation, had been treated by resection, alcohol injection, or palliation. Overall 5-survival rate for the group according to the Kaplan-Meier analysis was 65%, and for the 12 patients with recurrent disease, the 5-year survival rate was 40%.

COMMENT

Treatment of patients with HCC remains a clinical challenge. Liver resection, when possible, is usually considered to be the most effective treatment; however, the number of candidates suitable for surgery is limited, and surgery, even if potentially curative, is often followed by local recurrences. It has been estimated that 60% of the late deaths after radical surgery were due to cancer recurrence and that two thirds of tumor recurrences in the residual liver were seen during the first 1.5 years after liver resection. Treatment remains a problem even when tumors are diagnosed early, which is now more frequently the case than in the past because of the considerable progress in hepatic imaging. Cure can be achieved only by complete surgical excision, but the surgeon must also attempt to avoid later recurrence of the disease.

A recent report by Lau et al showed that when 131I-lipiodol was given after curative hepatic resection for HCC there was a significant decrease in the rate of recurrence and an increase in both the disease-free and overall survival rates. The overall survival rates for their treatment group were similar to our results at 3 years (86.4% vs 86%) and 5 years (75% vs 65%).

A pathological study of 80 consecutive cirrhotic liver explants without detectable HCC before liver transplantation has demonstrated a high prevalence of undetected multifocal small tumors and high-grade dysplastic nodules. Appreciation of this observation in the decision-making analysis has led to growing evidence that for patients with cirrhosis and small tumors liver replacement is probably the treatment of choice, since it cures both the tumor and the underlying disease. However, the subject is still controversial, and liver resection remains the best management for resectable tumors in patients with noncirrhotic disease and probably also in many patients with cirrhotic disease with large tumors and adequate parenchymal reserve. Moreover, considering the limited number of donors, there are powerful arguments to anticipate that the ideal treatment for patients with operable tumors is not only resection but also some form of adjuvant or neoadjuvant therapy targeted at prevention of tumor recurrence. It has been demonstrated that, following hepatic arterial injection of radiolabeled lipiodol, activity remains high within the tumors while being cleared from the normal liver to be excreted in the urine. There is little doubt that injection of lipiodol into the hepatic artery is not only effective for aiding in the diagnosis of HCC by postlipiodol CT but also has by itself some kind of therapeutic efficacy. Moreover, results of transcatheter oily chemoembolization were comparable at 5 years with those of resection and transplantation in a retrospective series. The aim of the interstitial therapy with 131I-lipiodol is to deliver a high concentration of radiation within the microscopic residual disease without the adverse effect of concomitant radiation to the neighboring normal tissue. Manipulation of radiation for liver disease may seem hazardous, considering the risk of unexpected adverse effects; however, the experience obtained with the palliation for unresectable HCC has failed to demonstrate any complication due to the injection of 131I-lipiodol.

The protocol included a second treatment with intra-arterial 131I-lipiodol after 2 years of disease-free survival. This may further help control macroscopic dysplastic changes or HCC but remains only a theoretical advantage. The results of this pilot study and that of Lau et al suggest a benefit of adjuvant interstitial therapy with 131I-lipiodol after curative resection for HCC in lowering the risk of tumor recurrence. A randomized, multicenter prospective trial comparing patients treated with intra-arterial 131I-lipiodol with a nontreated group will be the next step of this investigation.

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REFERENCES