Transcatheter Arterial Embolization in Hepatocellular Carcinoma

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INTRODUCTION

Hepatocellular carcinoma (HCC) or hepatoma is a relatively common malignant tumor in Indoncica and Asian countries, and patients with this neoplasm have a poor prognosis. The first choice of treatment is hepatectomy, but most cases are considered inoperable due to extreme tumor extention at the time of diagnosis.

According to the report of The Liver Cancer Study Group of Japan (1979), only 9% of hepatoma patients underwent hepatectomy. The one-year survival rate after surgery was only 28%. Chemotherapy produced the one-year survival rate 7% and the mean length of survival was 5-6 months.

Many hospitals in Japan have performed transcatheter arterial embolization (TAE) in cases of unresectable hepatoma which demonstrated far more satisfactory results than other existing treatment. According to Yamada et al.

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mutative one-year survival rate was 44% by TAE. Charnas et al. (1985) demonstrated that the results of TAE in their cases of which median survival rate was 17.4 months in cases of hepatoma. In the development of TAE combined with anticancer drugs and iodized oil showed the results of treatment was better (Kohayashi et al., 1986; Yoshino et al., 1982).

Equipments
1. Angiographic unit of X-ray machine for fluoroscopy and radiography.
2. Film changer (AUT, FUCT).
3. Automatic injector.
4. Life saving equipment in the angiographic room.

Materials for TAE
1. Catheters
   a. 5-6 F, 80 cm length, radiopaque
   b. Many types of catheters:
      - Cobra head
      - Modified Shepherd Hook (e.g. SHK)
      - RH type and modified RH (e.g Takekawa No. 2)
      - Loop-the loop
      - etc.

2. Guide wires
   a. Same is the same as each catheter (size of lumen)
   b. Straight tip, curved tip, and deflecting type tip
   c. Stainless steel and heparin-coated
   d. Special coating (Raflovus, Trevano).

3. Introcer:
   Introcer, used for exchanging the catheter and guide wire, will be located at the puncture site of the femoral artery, usually on the right side. The introcisers usually have a checkvalve mechanism (leak-proof).

4. Contrast media
   b. Ionic contrast media: Angiografin, Urografin, Hexabrix.
   Non-ionic contrast media is still expensive, but the side-effects is much milder and the diagnostic quality is superior to the ionic (Uchida et al., 1987).

5. Embolic agents
   a. Gelfoam (Upjohn Company, Kalamazoo, Michigan, USA). Non-initiating and non-antibiotic gelatin sponge. This agent is used very commonly. There are two types: block and powder. Spougol is quite similar to gelfoam.
   b. Lipiodol (Laboratoires Bertrand-Guerbet, Aulnay-sous-bois, France). Iodinated ethyl esters of the fatty acids of poppy seed oil. Lipiodol is very popular recently as a vehicle of anticancer drugs.
c. Ivalon (Unipoint Industries, High Paint, NC 27260, USA). Polyvinyl alcohol foam particles. Ivalon can be used in combination with some other material in the treatment of hepatic neoplasms. According to Miller (1987) Ivalon may have only a temporary occlusive effect in hepatic artery. Talavarry et al. (1974) injected Ivalon to stop bleeding in iliac artery and preventing fatal hemorrhage.

d. Cotton tail and wool coil (Gianutroco). Stainless steel wire with cotton or wool. This mechanical device was developed by Gianutroco et al. in 1975. Cotton tails were used in smaller arteries and wool coils for larger vessels (Gianutroco et al., 1975). Combination of steel coil with other embolic material was used by Chuang & Wallace (1981) for proximal occlusion of hepatic artery in treatment of hepatic neoplasms. Tuncador et al. (1979) reported displacement of stainless steel coil from left renal artery to common femoral artery.

e. Ephiboil (Ethicon GmbH, Norderstedt, West Germany). Viscous emulsion containing the protein zein, oleum papaveris, contrast medium and alcohol. Ephiboil is a radiopaque liquid with a honey-like viscosity. Once in contact with water, the protein component of Ephiboil precipitates and forms a chewing gum-like material. The alcohol component of Ephiboil acts only as a solvent, and is therefore not responsible for its vascular occlusive effect. For TAE, Ephiboil should be warmed to body temperature and should be injected in small quantities (0.5 – 1.5 ml) (Jaschke & Hoevels, 1980).

f. Ethiodol (Cave Laboratories, Meville, N. Y.). Ethyl esters of fatty acids of poppy seed oil and contains 57% iodine. Ethiodol was used combine with anticancer drugs by Yumoto et al. (1985) and Ohashi et al. (1989).

g. Ocycel (Parke-Davis & Co). Absorbable cellulose. There are two ops: Ocycel 80 and Ocycel 100.

h. Autologous clot and subcutaneous tissue. Effective in the control of various form of benign bleeding, it has relatively short life span (hours and days) (Goldstein et al., 1976).

i. Absolute alcohol. Intraarterial injection of alcohol produces sludging of blood corpuscles, coagulation of protein, arterial spasm and intimal damage, which results in thrombosis and arterial occlusion, perivascular leukocyte infiltration and perineuradial and perivascular fibrosis. The optimal indications for the use of alcohol for TAE are still to be established (Wallace et al., 1984), but alcohol has been used for treating other tumors or bleeding. Jaschke & Hoevels (1980) did not recommend the alcohol for hepatic arterial occlusion because alcohol produced many complications.

j. Bucrylate, isobutyl 2-cyanoacrylate. Mostly experimental, but some used it clinically.

6. Anticancer drugs
Combination of TAE and anticancer drugs injection namely chemo-embolization. Anticancer drug is mixed with Lipiodol suspension or Gelfoam before injecting. Adriamycin and Mitomycin C are used very commonly in
the procedure. Other drugs may be administered. The dosage of anticancer drugs is as follows:

- Adriamycin 10 – 40 mg
- Mitomycin C 10 – 20 mg
- Cisplatin (CDDP) 100 mg
- 5-Fluorouracil 500 mg
- Cytosine arabinoside 25 mg
- Echoposid under investigation.

Transcatheter arterial embolization technique

1. Transfemoral approach for inserting the catheter and guide wire. Local anesthesia.
2. Selective arteriography in celiac trunk or hepatic artery.
3. Arterial portography via superior mesenteric artery (SMA). Inject Prostaglandin E1 (PGE1) into SMA before injecting contrast medium. Prostaglandin F2 can be used, but slightly more stimulating the bowel movement (peristalsis).
4. Preparation of embolic agent and anticancer drugs (Lipiodol, Adriamycin, Mitomycin C, or Cisplatin).
5. Embolic agent and anticancer drugs is injected slowly under control of fluoroscopy, into feeder arteries or proper hepatic artery.
6. The mixture of Delfon pieces immersed in the contrast medium is injected into feeder arteries after Lipiodol. Amount of Lipiodol: smaller amount than 10–15 ml would be safer, because injection of a larger amount than 15 ml or so may cause embolization of portal vein branches.
7. If the patient feels pain in the right upper quadrant, morphine or analgesic agent such as fentanyl (Pentazocine) 15 mg i. m. may be given.

Photographic technique

Position: supine
Projection: anteroposterior (AP)

1. Celiac trunk or hepatic artery
   a. Contrast medium:
      - rate: 6 – 8.5 ml/s
      - total: 25 – 35 ml
   b. Film:
      - 2 films/sec for 3 s
      - 1 film/sec for 5 s
      - 1 film/sec for 12 s

2. Arterial portography
   Injection of PGE 1 20–40 mg i. a. or PGE 2 200 mg i. a.
   a. Contrast medium:
      - rate: 6–9 ml/s
      - total: 40 ml
b. Film:
   - 1 film/ s for 7 s
   - 1 film/2 s for 16 s
4. Intra-Arterial Digital Subtraction Angiography (IADSA) would be a nice set up to check the degree of occlusion of the artery.

Indications
Indications of TAE in hepatoma are:
1. Inoperable hepatoma (Yamada et al., 1983).
2. Preoperative resectable hepatoma (Nakamura et al., 1983).
3. Hepatoma with abdominal bleeding (Takekawa et al., 1979).
4. Recurrent hepatoma (Takekawa et al., 1985).
5. To inhibit tumor growth, relieve pain and perhaps to stimulate an immune response to ischemic neoplasm (Chuang & Wallace, 1980).

Criteria of patients
The criteria for patients who will be treated by TAE and anticancer drugs (Yang et al., 1980; Takekawa, 1989):
1. Histology proven either by cytology or biopsy, or with strong proof by AFP.
2. Clinical performance status of Child’s A and B patients.
3. No main portal vein invasion causing obstruction, as seen on an angiogram and/or CT.
4. No distant metastasis.
5. No severely elevated total bilirubin.
6. No severe renal damage.
7. No remarkable esophageal varices.

Contraindications
1. Hepatic cirrhosis with severe hepatic dysfunction.
2. Tumor thrombus in main portal vein and or its branches.
3. Very large tumor with many feeder arteries.

Complications
1. Pain, usually in the right hypochondriac region or right upper abdomen, has been reported by many authors. Pain in the epigastrium or left hypochondriac may indicate acute pancreatitis from reperfusion of embolic materials.
2. Fever, due to necrosis of tumor or liver tissue.
3. Nausea and vomiting.
4. Increase in ascites (Yamada et al., 1983).
5. Necrosis of gallbladder, due to migration of embolic agent into the cystic artery (Miller & Mineau, 1985; Kuroda et al., 1983; Onodera et al., 1984; Takayasu et al., 1985).
7. Splenic infarction (Takayasu et al., 1984).
10. Progression of cirrhosis of the liver.

**Post-embolization management**

1. Pain: a. High dose meperidine or morphine during the first 48 hours.
   b. Scopolamine during the first 3 days.
   c. Analgesic suppository (Diazepam, Cericin).
3. Fever: a. Aspirin or acetaminophen within a few days.
   b. Steroid 3-2 days, suppository is easier to use.

This management of post-embolization syndrome was modified from Clouse & Lee (1984) and Takekawa (1989).

**DISCUSSION**

Transcatheter arterial embolization (TAE) was first reported by Goldstein et al. (1976), and then reported by many authors as an effective therapy for liver malignancy (Chuang & Wallace, 1981; Charnsangavej et al., 1983; Yamada et al., 1985). The principal of TAE technique is to obliterate the feeder arteries for tumor tissues, and cause necrosis of the tumor.

The normal hepatic parenchyma has a dual blood supply, with 25-30% deriving from the hepatic artery and 70-75% from the portal vein. Primary and secondary hepatic neoplasm receive 90% of their blood supply from the hepatic artery. Portal vein blood supply protects the normal hepatic tissue from necrosis in embolization of hepatic artery. Fujiwara et al. (1986) reported a case of hepaticoma with main blood supply from the portal vein. In this case, celiac arteriography showed a poor arterial supply but a rich portal supply as observed at percutaneous transhepatic portography. Devascularization of a hepatic neoplasm could be achieved percutaneously by combined peripheral embolization of particular material (Gelfoam/Sponge/ etc.) and central occlusion with a stainless steel coil (Chuang & Wallace, 1980). Hepatic artery collaterals (intrahepatic and extrahepatic) could be demonstrated following embolization and occlusion (Charnsangavej et al., 1985), and the presence of these collaterals was significant in the management of hepatic neoplasms.
In hypervascular hepatic tumor the inferior phrenic arteries represent a source of collateral blood flow for neoplasm, and these arteries should be embolized with minimal complications. There was no evidence of diaphragmatic necrosis except possibly in the patient who developed pleural effusion after embolization (Duprat et al., 1988).

In performing TAE for hepatoma, it is important to obtain information as detailed as possible about the invasion of the tumor into the portal vein, and for this purpose it is necessary to visualize the intrahepatic portal vein as clearly as possible. Intraarterial portography is done via superior mesenteric artery (SMA). Bolus injection of Prostaphlin F 1 (PGE 1) into SMA produces slight dilatation of the artery and blood flow is markedly increased. The portal vein is first seen 3 to 10 seconds (mean 5 seconds) after the beginning of contrast medium injection, with optimal opacification after 6 to 15 seconds (mean 10 seconds). The quality of the portal vein opacification is greatly improved after using PCE 1 (Jonsson et al., 1977). According to investigation of Nakamura et al. (1987), visualization of intrahepatic portal vein was improved by injection of PGE 1 and balloon occluding superior mesenteric arteriography. By this method there was neither a rebound of the catheter into the aorta nor a backflow of contrast medium into the aorta. The sharpest image of the intrahepatic portal vein was obtained from 6 to 12 seconds after injection of filming. Prostaphlin F 2 a had the same effect with PGE 1 and the price was cheaper, but slightly more stimulating to the pericardial of the bowel (Takekawa, 1989).

The results of treatment of hepatoma have been reported by many authors, which can be seen is TABLE 1 as a summary of those results. The methods of therapy and evaluation were different by different authors. Combination of TAE and antineoplastic drugs showed higher survival rate than TAE or antineoplastic drug alone. Adriamycin and Mitomycin C were used very commonly, but Capcizacin (CDHP), 5-Fluorouracil derivative and Fluoridine were occasionally used.

To improve and intensify the anticancer drugs in the tumor tissue iodized oil (Lipiodol) is used as a vehicle. Anticancer drugs were suspended in iodized oil with a dispersing stabilize aluminim monostearate (Nakakuma et al., 1983; Kobayashi et al., 1986; Yدوon et al., 1985), and injected into hepatic artery or its branches. Lipiodol particles filled all branches of hepatic artery of a diameter over 25 um and Lipiodol retention in the tumor tissue could be detected more than one year by abdomen plain film or CT examination. Level of biologic anti-cancer drug activity in tumor tissue was higher compared to normal hepatic tissue (Nakakuma et al., 1983).

In the normal hepatic tissue Lipiodol disappears very early. The washed out Lipiodol in normal hepatic tissue probably passed into the sinusoidal spaces and slowly permeated interlobular liver duct by the reticuloendothelial system or the liver (Nakakuma et al., 1985), and the hepatic lymphatic (Yumoto et al., 1985). According to the study by Miller et al. (1987) it was shown that early clearance of particulate neoplasm might possibly be caused by extrinsic hepatic ischemia from microemboli or by direct phagostosis by Kupfer cells and there was no evidence that iodized oil was cleared by hepatic lymphatics.

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<table>
<thead>
<tr>
<th>Authors</th>
<th>Cases</th>
<th>TAE</th>
<th>Anticancer</th>
<th>Survive</th>
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<tbody>
<tr>
<td>Charnaigov et al. (1988)</td>
<td>11</td>
<td>FAM</td>
<td>N/A</td>
<td>17.4 mos. (median)</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td></td>
<td>N/A</td>
<td>12.5 mos. (median)</td>
</tr>
<tr>
<td>Yanada et al. (1983)</td>
<td>129</td>
<td>10mg</td>
<td>90mg</td>
<td>44% 1 yr.</td>
</tr>
<tr>
<td>Ohshu et al. (1985)</td>
<td>97</td>
<td></td>
<td>N/A</td>
<td>89% 6 mos.</td>
</tr>
<tr>
<td>Kohsay et al. (1988)</td>
<td>41</td>
<td>10mg</td>
<td>10-42mg</td>
<td>60% 1 yr.</td>
</tr>
<tr>
<td>Yang et al. (1986)</td>
<td>39</td>
<td></td>
<td>10mg</td>
<td>49% 1 yr.</td>
</tr>
<tr>
<td>Hira et al. (1988)</td>
<td>191</td>
<td>10mg</td>
<td>10-40mg</td>
<td>22% 1 yr.</td>
</tr>
<tr>
<td>Takayanu et al. (1988)</td>
<td>180</td>
<td></td>
<td>10mg</td>
<td>66.2% 1 yr.</td>
</tr>
<tr>
<td></td>
<td>89</td>
<td></td>
<td>10mg</td>
<td>36.5% 2 yrs.</td>
</tr>
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Note: FAM = Fluoradidion, Adriamycine, Mitomycine C, MMC = Mitomycine C, ADR = Adriamycine, MMC = Mitomycine C, MFC = Mitomycine C, 5-fluorouracile, Cytosine arboisolate, APC = Adriamycine, 5-fluorouracile, Cytosine arboisolate, ASMOC = Adriamycine and/or Mitomycine C suspended in iodised oil (Lipiodol).

The washed-out Lipiodol in tumor tissue disappears very slowly. The vessels in tumor tissue does not have sufficient blood flow to clear away the adhesive Lipiodol, the blood flow is slow through the tortuous and irregular neoplastic vessels, which often lack both a muscular and elastic lamelle (Nakakuma et al., 1985). The disappearance of Lipiodol from the injected artery seems to depend on washout by flowing blood in a nonmucous tissue.

The other advantage of the long period of selective retention of an oily contrast medium or Lipiodol in hepatic tumor is to aid in the diagnosis of these tumors. This method is considered to be effective not only for treatment of hepatic tumor but also for evaluation of post-TAE changes in the tumor and diagnosis of small daughter nodules (which could not be diagnosed by angiography and/or CT prior to TAE) due to the long-term accumulation of iodinated oil in tumor tissue (Nakakuma et al., 1985; Ohshu et al., 1985; Yamao et al., 1985). But uptake and retention of Lipiodol are not characteristic of the hepatic malignant tumors, because uptake and retention up to 5 months was demonstrated in hepatic carcinomas and in hepatocellular carcinoma and in the other cases of the main tumor significantly.

Prognosis of hepatoma after TAE is still not completely satisfactory, and 5-year survival rate is hardly attained. The prognosis is influenced by many factors. According to Takayanu et al. (1989), the size of the main tumor significantly
influenced the prognosis following TAE, whereas the frequency of TAE, intra-hepatic metastasis and degree of liver dysfunction showed a slight correlation.

CONCLUSION

Vascular catheterization technique has been used not only for diagnostic purposes but also in treating certain diseases. Current uses of the procedure include transcatheter arterial embolization (TAE) in inoperable hepatoma due to the advanced stage of the tumor and/ or on hepatic cirrhosis.

The materials for TAE and angiographic facilities in a hospital are needed for performing TAE. Selection of patients to be a candidate for TAE is very important because detection of contraindications prior to TAE should be done very carefully and we have to be aware of complications that may occur. Application of TAE technique to the patient sometimes is not very easy but this problem can be solved by obtaining experience in angiography that requires a certain period.

The better result of treatment is obtained by combination of TAE and anticancer drugs. Prognosis after TAE is still not completely satisfactory, but the patient has a longer survival time. Therefore, TAE should be seriously considered in the treatment of patients with advanced or inoperable hepatocellular carcinoma to prolong their life with good quality.

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