RADIOENDOVASCULAR CHEMOEMBOLIZATION OF HEPATIC ARTERY IS AN ADVANCED TECHNIQUE OF REGIONAL CHEMOTHERAPY IN MALIGNANT HEPATIC TUMORS (REVIEW)

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A.A. Seregin, Head of the Diagnostic and Therapy Interventional Radiology Department

Privolgzhsky District Medical Center of Federal Medico-Biologic Agency of Russia,
Nizhne-Volzhskaya naberezhnaya St., 2, Nizhny Novgorod, Russian Federation, 603005

The review concerns one of the urgent problems of modern oncology: the management of patients with unresectable hepatic cancer. The capabilities and advantages of one of the most common radioendovascular techniques — transcatheter chemoembolization of hepatic artery — have been described in detail. We have shown morphofunctional principles of chemoembolization, compared the properties of the most common chemoembolic agents: lipiodol (an oil chemoembolic agent), saturable microspheres (Hepasphere, DS Bead). There has been considered the spectrum of diseases and conditions, when hepatic artery chemoembolization is reasonable, as well as the capabilities of the technique used as adjunctive therapy. We have indicated the complications resulted from interventional procedures, and suggested our own classification of basic complications. The criteria for chemoembolization assessment have been given.

Key words: hepatic artery radioendovascular chemoembolization; unresectable hepatic tumors; transcatheter chemoembolization of hepatic artery.

Two main forms are distinguished in the structure of malignant neoplasms: primary cancer (hepatocellular cancer, hepatoma), and metastatic damage. Primary liver cancer ranks 6th (5.7%) among all registered cases of cancer in the structure of oncological morbidity [1–10]. Metastatic liver damage according to autopsy results is observed in 20–70% of oncological patients [1–3, 11, 12–14]. The most common source of metastasizing (more than 80%) is cancer of the colon and rectum [4–7, 11–17]. Five-year survival rate of the patients both with primary and metastatic cancer is extremely low and amounts to 5–6% [11, 12, 16–22].

The classic method of treating patients with malignant liver damage includes the following stages: surgical removal of the primary tumor focus and resection of the liver with metastases, and systemic chemotherapeutical treatment to eliminate or reduce the volume of the pathological process in the liver, also aiming to achieve the operable condition [11, 12, 17–19, 23–29]. When the diagnosis of primary cancer or metastasizing is established, radical operation is, however, possible only in 5–15% of patients [11, 12, 21, 22, 25]. Recurrence and/or progressing of metastatic lesion after liver resection is observed in 20–60% of people, only in one third of them a second operation being possible [11, 12, 22, 26–31].

Evidently, a palliative chemotherapy is required for more than 70% of patients with malignant liver tumors. However, the efficacy of systemic chemotherapy in inoperable damage does not exceed 20–30% in 3–4 months survival even if combinations of several preparations are used [17, 18, 22, 26, 28, 29]. In intravenous introduction of chemopreparations therapeutical concentration is likely to be reached only for a short time, not affecting adequately tumor cells, and marked disorders of the liver detoxication function restrict the application of larger doses of antitumor medications [16, 18, 22–24, 26, 32–36].

Thus, in order to improve the remote results of treatment of patients with unresectable liver tumors it is necessary to solve the following tasks: to achieve optimal concentration of the medication in the tumor node, to

For contacts: Seregin Andrey Anatolievich, phone +7 920-061-22-92; e-mail: andreiseregin@yandex.ru

provide prolong action of chemopreparation in the focus, to induce ischemic necrosis of the tumor [37–46].

One of the solutions to this problem is introduction into clinical practice the methods of regional chemotherapy: radioendovascular chemoembolization of hepatic artery (CEHA). Japanese scientists R. Yamada et al. (1979), the official authors of this method, introduced a cut gelatin sponge, saturated with 10 mg of mitomycin C or 20 mg of adriamycin into the branch of the liver artery supplying blood to the tumor in unresectable hepatomas [43, 46]. T. Konno et al. (1982) were the first to use lypiodol, which possessed two unique properties: ability to absorb chemoprparations and accumulate in the liver tumors which enabled to reach a double effect with only one infusion — local delivery of preparation and temporary embolization of the vessels [47, 48].

It should be mentioned that there have been some prior publications on CEHA application. In 1973 a French doctor C. Regensberg and his colleagues published the results of 250 performed radioendovascular embolisations of hepatic arteries in patients with liver metastases using Caryolysine suspension, hemostatic sponge and Thrombovar [49]. A cytostatic agent Caryolysine exerted local chemotherapeutical action, while embolization of the vessels by the hemostatic sponge and Thrombovar resulted in tumor node necrosis. Actually, this was the first documented clinical application of the double local action on the tumor: infusion of the chemopreparation and mechanical embolization of the arteries supplying the nodes.

The efficacy of radioendovascular CEHA depends on the blood supply of the liver and tumor node. A normal parenchyma of the liver has double blood supply: from the portal vein — 70% of the total blood volume, entering the liver, and 30% from the hepatic artery. Blood supply of the tumor nodes occurs mainly from the branches of the hepatic artery [47, 48, 50]. Such vascular architectonics allows to introduce selectively high doses of chemopreparation directly to the tumor, preventing or significantly reducing its effect on the healthy liver cells [47, 48, 51–53].

A favorable result of this procedure is obtained due to the following mechanisms: selective introduction of chemopreparations in the damaged area leading to the decrease of their toxic effect; prolonged high concentration of the drugs, and, as a consequence, their stronger action on the tumor because of termination or significant reduction of washing the preparation out from the tumor; damage to the tumor and the development of its ischemic necrosis [43–46, 51–55].

Preparations are introduced with the help of substances, called preparation-carriers, which possess a marked absorbing capability [46, 48, 52, 56–60]. As it has been mentioned above, Lipiodol, a iodized complex ester, obtained from the poppy seed oil, is widely used in a clinical practice. Lipiodol retains preparations for a long period of time and then slowly releases them, enabling the delivery of drugs to the tumor node in a high concentration and a long action directly on the damaged area — the so-called oil CEHA [56, 57, 60–64].

The oil chemoembolizate penetrates both the tumor and healthy liver tissue. Owing to the presence of the muscular layer the healthy parenchymal arterial bloodstream provides movement and quick elimination of the oil contrast preparation. Pathological tumor vessels do not have a muscular layer which results in prolong retention of chemoembolizate in the tumor [56, 62, 65, 66]. To reduce the blood flow to a more extent, oil embolization is supplemented by a mechanical one, using a hemostatic sponge. Occlusion of the arterial blood flow after introduction of Lipiodol emulsion with chemopreparation prolongs the time of the chemopreparation presence in the damaged area, and also causes necrosis of the tumor node [48, 51–53, 67–71].

The next step in the development of the chemoembolization method was the discovery and introduction of loaded microspheres into the clinical practice. At present two types of microspheres are known: loaded directly before the introduction into the arterial bloodstream — Hepasphere (Biosphere Medical Inc., France) and the so-called overloaded ones, i.e. enriched with chemiopreparation in the course of their production — DC Bead (Biocompatibles, Great Britain) [72–83].

Superabsorbing Hepaspheres are biocompatible, hydrophilic (absorbing), unresorbable microspheres, manufactured from acrylic copolymer, and possessing a unique property to take in fluid in the volumes 64 times exceeding the volume of microspheres in a dry form. The size of dry microspheres varies from 30 to 200 μm, and in the saturated form from 120 to 800 μm [72–83].

Microspheres DC Bead are made from polymeric hydrogel, modified by the addition of sulfonic acid, allowing to produce spherical particles of different dimensions by polymerization, are loaded then with doxorubicin preparation directly in the manufacturing process [77–80, 82, 83].

When microspheres are introduced, all the above-mentioned mechanisms are realized [77, 80–82, 84, 85].

Doxorubicin, Irinotecan, Gemzar are commonly used for monotherapy. While for polychemotherapy it is reasonable to use a combination of doxorubicin, cisplastin and Mitomycin, for example, doxorubicin (or Adreamycin) — 50 mg, citoplastin — 100 mg and Mitomycin C — 10 mg, which are diluted in 10 mg of water-dissolved contrast agent, and are emulsified then in the equivalent volume of Lipiodol [65, 66, 77, 80, 86–101].

By the present time, a range of diseases and conditions in which it is reasonable to apply CEHA has been outlined: unresectable hepatocellular cancer, cholangiocarcinoma, metastases from the breast cancer, neuroendocrine tumors, colorectal cancer [52, 56, 61, 71, 77, 86, 90, 102–111].

CEHA can also be used as an adjunctive therapy prior or following the radiofrequency ablation [112–117].

It is not recommended to perform this procedure prior the operation in patients with resectable liver damage in order to reduce blood loss or prevent implantation metastases [114, 116].

Absolute contraindications are: resectable tumor, diffuse tumor process, active systemic infection, continuing bleeding, class Child-Pugh C, leucopenia (a number of leukocytes less than 1000/ml), prothrombin time less than 40%, heart failure (left ventricular ejection fraction less than 50%), kidney insufficiency (creatinine more than 177 mmol/L), incorrectable sensitivity to the contrast agent, functional status according to ECOG Performance status scale — higher than 3, encephalopathy [52, 65, 71, 77, 81, 82, 86, 96, 114, 115, 118–126].

Some authors place cardiac and kidney insufficiency, as well as encephalopathy to the category of relative contraindications [119, 122, 125]. Involvement of over 50% of the liver volume, metastases of other localizations, growth of the tumor into the inferior vena cava and the right atrium, ascites, marked thrombocytopenia, previous operation on portocaval anastomosis are also considered by the others to be relative contraindications [82, 86, 126–129].

Referred to the group of relative contraindications are cases with the development of liver insufficiency: increase of total bilirubin to more than 34.2 μmol/L [77, 101–103], according to other data — 50–70 μmol/L [71, 73, 82, 84, 130, 131], lactatdehydrogenase — more than 425 Units/L [82, 132], 5-fold increase of aminotransferase level compared to the norm [130, 133, 134]. Portal vein thrombosis is not considered to be a contraindication for CEHA [125, 131, 134–142].

Thus, there are no serious contradictions in defining indications and contraindications to the application of CEHA. Indications to intervention tend to become wider. With the advent of new hepatoprotectors, chemoembolization is finding its application in patients with the marked hepatic insufficiency [133, 134, 136]. It should be noted, that indications to the application of microspheres are more limited than oil embolization; the authors explain it only by the absence of a sufficient evidence base [73, 94, 137–139].

Having the experience of more than 500 embolizations we join the opinion of J. Gates et al. (1999) in defining indications: sufficient functional reserves of the liver (bilirubin not exceeding 70 mmol/L), hemoglobin — more than 80 g/L, absence of extrahepatic extension of the tumor, morphological forms of the tumor in which chemoembolization is effective [124].

Complications of the intervention are studied well enough, and are observed in 4–7 to 5–10% of cases [143–171]. The majority of the authors do not classify the complications, simply enumerate them. Some investigators divide the complications into vascular and nonvascular [143, 145, 147, 153].

We distinguish the complications, associated with non target extrahepatic infusion of embolization material: into the gastric arteries (acute gastric ulcer), gastric-duodenal and pancreatic-duodenal arteries (acute pancreatitis), cystic artery (acute cholecystitis), inferior phrenic artery (pleurisy, atelectasis of the lung), intercostal arteries [143–145, 152–154]. In our investigation acute pancreatitis occurred in 4 patients, superficial necrosis of the gastric mucous membrane — in 1. Conservative treatment resulted in significant improvement.

The next group includes complications caused by the toxic effect of the chemopreparations and contrast agents: anemia (2–7%), progressing hepatic insufficiency (4–38%), kidney insufficiency (9%) [143, 147, 148, 150, 151, 155].

The third group comprises complications caused by manipulations on the vessels: extensive hematoma in the paracentesis area, generation of the false aneurism of the femoral artery, dissection of the hepatic artery by the wire guide or catheter [143, 147]. In our practice vascular complications were noted in 5.6% of cases. Dissection of the hepatic artery intima was in 8 patients, and only in 1 case the procedure was discontinued because of this event.

The rest complications are referred to the group of rare cases: pulmonary thromboembolism when embolizate enters the lungs via arteriovenous shunts [156–160], embolism of the cerebral arteries [143, 147, 149], bleeding from the various veins of the esophagus due to the increased pressure in the system of the portal vein [147].

There are authors who consider the so-called post-embolization syndrome to be a complication: elevation of the body temperature, pains in the epigastrium, nausea, vomiting, some worsening of the hepatocellular insufficiency. Postembolization syndrome develops in 90–100% of patents and lasts from 2 days to 3 weeks [143, 146, 147, 170–174].

We think that this condition is not a complication of the intervention, but is a natural state after CEHA. Evidently, all three mechanisms of CEHA action, as well as toxic, systemic effect of the antitumor preparation are the causes of its development. Post-embolization syndrome phenomena are successfully relieved by symptomatic drug therapy.

Criteria RECIST (Response Evaluation Criteria in Solid Tumors) are most commonly used to assess the results of CEHA. According to this scheme a complete or partial effect occurs when the tumor volume reduced by more than 25%; stable disease — in case of tumor volume reduction by less than 25%, or no increase of the tumor and new foci in the liver are observed; progressive disease means the increase of the tumor size or appearance of new foci in the liver [26, 27, 33].

Recently the results of 4 large randomized trials of treating inoperable patients have been published [27, 81, 128, 175]. The most impressive is the work performed by the Japanese scientists K. Takayasu and his colleagues (2006) covering 8500 patients [128].

In the majority of other investigations the results obtained were quite comparable [175–196]: a complete or partial response after the third or more courses equals to 43–80% (according to our own observations — 70.0%), two-year survival — 31–80% (our data — 52.3%), median of survival — 12.6 to 34 months (in our observations — 22.4 months) [175, 191–196].

In the study PRCISION V (n=212) the results of embolization by superloaded microspheres (group 1) and oil chemoembolization (group 2) were compared. A complete or partial response was observed in group 1 (in 52% of patients), in group 2 — in 43% [81]. Other authors also note some advantage of procedures with microsphere embolization [83, 85, 197–200].

Conclusion. Radioendovascular chemoembolization of the hepatic arteries is a variant of choice in helping the patients with inoperable liver cancer, and owing to its high efficacy and relative safety allows to achieve improvement and stabilization in 45–75% of cases.

A long-lasting effect of chemoembolization is explained by realization of the three main mechanisms of treatment: creation of locally high concentration of the selectively infused medication, prolonged presence of the chemopreparation in the focus, and induction of ischemic necrosis of the tumor.

Application of microspheres gives somewhat better results than a classic oil chemoembolization, however more experience should be gained to answer the question in what clinical cases embolization by microspheres is most effective.

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