Lymphatic Chemotherapy for Alimentary Tract Malignant Tumor

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Alimentary tract malignant tumor is a familiar worldwide disease. Operation is still the mainly therapeutic means. Lymphatic metastasis is one of mainly spread modes and is the important reason for unsatisfactorily operative therapy and postoperative recurrence. In order to increase operative cure rate, it is very important for antitumor therapy in perioperative period. It is of great value for new adjuvant chemotherapy to decrease bioactivity, lessen implantation of cancer cell in operation and reduce postoperative recurrence. Lymphatic chemotherapy is regarded and adopted as a form of neoadjuvant chemotherapy by more and more clinical practitioners.

Significance of lymphatic chemotherapy

There is an affinity between lymphatic metastasis and the prognosis of alimentary tract malignant tumor. Lymphatic chemotherapy may further elevate survival rate. Some data indicate that lymphatic metastasis rate is 0–3% focused in mucosa of early gastric cancer, 20% in submucosa and about 70% in advanced gastric cancer. Five-year survival rate of patients undergoing radical resection without lymph node metastasis is 82.5%, that with 1–4 lymph nodes metastasis is 49.1%, 5–9 lymph nodes metastasis is 34.5% and that of exceeding 10 lymph nodes metastasis is 9%[1]. Patients died of lymph node recurrence account for 20% of all death cases after radical operation of gastric cancer[2]. Patients with local recurrence account for about 40% of all recurrent cases in colon cancer, and those account for 52.6% in rectal cancer. The important reason for local recurrence is that the lymph nodes to where cancer cells metastasize are not dissected thoroughly. The effective chemotherapy may directly kill cancer tissue in lymphatic system, and prolong postoperative survival time accordingly.

Methods of improving therapeutic effect

The premise of ensuring the effect is the definite concentration of antineoplasm drugs. The higher concentration of medicine is in tissue, the better effect could be got. It is a reliable method of preventing lymphatic metastasis and recurrence that chemotherapy drugs congregate in lymphatic tissue and form a environment of local high concentration. The anti-tumor effect can be evaluated by detecting drug concentration in the tissue.

Intravenous administration is a traditional method and regarded as effective in chemotherapy of alimentary tract malignant tumors, but the problem of lymphatic metastasis is not resolved thoroughly. The big dosage of anti-tumor drugs can not be transported and congregated to peripheral lymph nodes of alimentary tract so as not to effectively kill the lymphatic metastasized cancer cells. And severe toxicity reactions of high dose of antineoplasm drug could occur.

This disadvantage of intravenous chemotherapy may be reduced by lymphatic chemotherapy. Beneficial explorations have been done in administration approach and dosage form of chemotherapy drug in order to increase antitumor drug concentration in lymphatic system, improve the effect of lymphatic chemotherapy and reduce general toxicity reaction.

Routes of lymphatic chemotherapy

Routes of lymphatic chemotherapy at present include intraarterial perfusion, submucous injection, intestinal perfusion, lymph node injection and lymphatic vessel perfusion. The satisfactory administration route is lymphatic vessel perfusion, by which higher concentration of chemotherapy drugs can directly enter the lymphatic system to contact with metastasized cancer cells and kill them. Pre-clinical and clinical experiments have testified that chemotherapy drugs perfused by lymph vessels could prevent and cure lymph node metastasis. Carr[3] used 5-fluorouracil (5-FU) to treat metastasized breast cancer in rat model with lymph vessel perfusion, the result is that lymph node metastasis was cured or prevented. Pankov[4] and Tarrat[5] separately treated ovary cancer, uterus cancer and cervical cancer by lymph vessel perfusion of anticancer

drugs, partial remission appeared in clinical manifestation, and some pathological alterations of cancer cells in lymph nodes also appeared, such as turgidity, vacuole formation and nuclear fissure. Moreover, Kovovin [6] and his colleagues compared the differences of lymph vessel administration and intravenous administration for preventing melanoma recurrence, and found that metastasis rate of lymphatic vessel administration was 15.7%, that of intravenous administration was 38.6% and there was a significant difference between two groups.

Because lymph vessels are very narrow in diameter, lymphography should be made routinely before lymph vessel perfusion. Iodine oil is usually adopt to make lymphography of lower limb. After that, lymph vessels are exposed, communicating branches are ligated, and tube is inserted for continuous infusion. It is difficult to find useful lymph vessels due to their distribution is reticular in lower limbs. So it is not feasible for some patients to use this method to perform lymphatic chemotherapy. In addition, lymph circumfluence of lower limbs does not passes through the alimentary tract, and that is the mainly reason why lymph vessel perfusion is not adopted to perform lymphatic chemotherapy for alimentary tract carcinoma. In order to develop this kind of therapy widely, many scholars have done many researches on administrative routs.

Jin Sik Min gave chemotherapy drugs via left gastric artery during operation and compared it with another group of administration via peripheral vein. The concentration of the former in perigastric lymph nodes was 9545 DPM which is much higher than 2516 DPM administered via elbow vein. The drug concentration in cancer tissue of the former was 5837 DPM, and the latter was only 2830 DPM. The drug concentration in liver of the former was also higher than the latter. It is beneficial to prevent liver metastasis which results from pressing and dissecting tumor in operation procedure, and it is effective to inhibit the spread of cancer cells via lymphatic system.

Drugs administered through alimentary tract could be absorbed by lymph, transported to lymph nodes where cancer cells accordingly were killed. Oral or rectal administration may be done in clinic. The method is simple and easily popularized. But the most drugs are mainly absorbed into bloodstream with this kind of administration, the concentrations of drugs into lymph system are not enough to reach the required treatment level and the drugs property of penetrating into the mucosa should also be considered when selected. 5–FU is given via the path commonly. Professor zhouxigeng[7] labeled 5–FU with isotope ^{14}C for tracking, gave it to patients through peripheral vein or rectal enema, detected its concentration and distribution in tissue, and compared the difference between the two administrations. He found that 5–FU concentrations in rectal wall and mesentery lymph nodes via rectal enema were far higher than traditional intravenous administration.

There are abundant and reticular lymph vessels in submucosa of alimentary tract. Once chemotherapy drug is injected into them, higher drug concentration and longer time would be remained in alimentary tract wall, cancer tissue and lymphatic tissue. And it may be injected by endoscope without injury in clinic. Shukla compared drug concentrations of cancer tissue, gastrointestinal tissue of pericancer, lymph nodes, liver and blood sample of portal vein after administrations via intestinal lumen, intratumor and peripheral vein respectively in 30 patients during gastrointestinal cancer operation procedures. He found that drug concentration of intratumor injection in all samples was the highest, that of intravenous administration took the second place and intraluminal administration was the lowest. It indicated that intratumor injection is the optimal method of adjuvant chemotherapy to prevent lymphatic metastasis and recurrence. We found that it is difficult for direct intratumor injection to reach therapeutic dose, because it is easy to induce tumor necrosis, breakdown and hemorrhage due to rigid and fragile texture of cancer tissue. Pericancer submucosa is so looser that it is suitable for drug administration with larger dose for the purpose of treatment.

Research on the form of dosage for lymphatic chemotherapy

At present, chemotherapy drugs in common use in clinic are frequently soluble agents. Whichever form of administration is adopted, drugs are mainly absorbed via blood. It is difficult to remain higher concentration in lymphatic tissue because the drugs infiltrate into surrounding tissue through the thin wall of lymphatic vessel even if soluble drugs are injected into lymph vessel. In addition, normal lymph node stroma is composed of hydroxide praline which is hydrophobic and unpolarized, so it is difficult for soluble agents to infiltrate into and congregate in lymph nodes, but easy to spread out of lymph vessels and enter into venous system [5].

Accordingly, a special kind of dosage form suitable for lymphatic chemotherapy should be explored in order to elevate drug concentration and improve therapeutic effect. Therefore, scholars have done many beneficial explorations and gained many achievements.

With the technique development of biosynthesis and degradation from the 1970s, antibody, liposome, polylactic acid and anticancer drugs have been integrated into several kinds of compounds, which help to increase anticancer drug concentration in lymphatic tissue because larger compounds are absorbed more easily by lymphatic tissue. Now the researches focus on 5-FU emulsion, mitomycin C (MMC) lipidosome, adriamycin (ADM) lipidosome.

5-FU is the metabolite of uracil, which belongs to cell cycle specific agent and is most sensitive to phase S of tumor growth. So it is necessary to contact with the tumor cells for a long time to gain the effect of inhibiting and killing them. Therefore, the therapeutic key of 5-FU is the effective drug concentration which should be kept and remained for a long time. The minimal effective concentration of 5-FU in tissue is 0.05-0.06ng/g, if it is exceeded, cancer cells existing in lymphatic tissue could be killed effectively. N1-(2 tetrahydrofuryl)-5-fluorouracil (FT-207) and its oil-in-water-type emulsion as well as its water-in-oil-type emulsion are administered orally for 8 patients after operations of gastric cancer by Hanaueu[8]. He observed that drug concentrations of lymph in thoracic ducts exceeded 0.06 ng/g without exception, and after oral administration of water-in-oil-type emulsion, the concentrations in lymph nodes and serums all exceeded those of FT-207 and its oil-in-water-type emulsion group from 30 minutes to 8 hours. This experiment indicated that FT-207 emulsion may distinctly increase the drug concentration of FT-207 absorbed in lymphatic tissue.

Professor Zhou xigeng[7] compared the concentration and the distribution of suppository and emulsion in tissue by applying isotope ^{14}C to label 5-FU for tracking, and also compared two administration routs of peripheral vein and rectal lumen. He found the concentrations produced by 5-FU emulsion in rectal wall and mesentery lymph nodes were all higher than suppository. This method was applied for 4 patients with low rectal cancer and drug concentration of cancer tissue in removed specimen was 3000 times of that in peripheral vein. Hirotoshi[9] compared the distributions of 5-FU emulsion and its solution which were administered via oral, intramural through the gastric serosa and submucous by endoscope. The drug concentrations of solution group were the lowest both in gastric wall and peripheral lymph nodes. After the first injecting 5-Fu solution into mucosa, drug concentration of the first group lymph nodes was 0.24ng/g and that of the second group lymph nodes was not detected. After injeced repeatedly, drug concentration of first group lymph nodes was 0.26ng/g and that of second group lymph nodes could also be detected.

MMC liposome was developed since 1983. Liposomes have many advantages as the carriers of anticancer agents such as high selectivity, good target, less adverse side effects, increasing therapeutic index and many kinds of administration routs, such as intravenous, subcutaneous, intramuscular, intraperitoneal, oral and local[10]. After this, ADM, cisplatin (CDDP), methotrexate (MTX), cytarabine (Ara-C) liposomes and so on have been studied and some progress has been made in preclinical and partly clinical application[11]. The similar researches in domestic began since 1990s, and the conclusion was similar. The drug concentrations of peripheral bloodstream and retroperitoneal lymph nodes were detected after ADM and Lipo-ADM was administered via lymphatic vessels of rabbit foot dorsal vein by Fengbibo [12]. He discovered that the peak concentration in peripheral blood of Lipo-ADM group was only 1/5 of water solution group, the drug concentration in lymph nodes in Lipo-ADM group was 2 times of the former and the pathologic alterations of the latter were more marked than the former. But liposome and other substance may be cleared by degrading or devoured by reticular endothelial system[13]. The biological distribution of liposome may be improved by altering its size, composition and charge, but Tokunaga[14] found the anticancer activity was decreased distinctively by further research.

Mitomycin C-dextran conjugate (MMC-D) was synthesized with dextran as carrier and 6-aminocaproic acid as linker by Kyoto university of Japan in the early 1980s, the pharmacokinetics characteristic of MMC was altered. It becomes an effective slow-released system of preventing and treating lymph node metastasis and the first pass effect of liver is avoided by local administration. MMC-D was injected into rat claw inoculated with leukemia by Takakura [15]. The drug concentration which could last 48 hours in lymph nodes was 50 times of that of MMC emulsion group. The weight

of lymph nodes undergoing MMC–D chemotherapy dropped remarkably.

Activated carbon absorbing chemotherapy may also be used for lymphatic chemotherapy. Domitsu [16] performed lymphatic chemotherapy with activated carbon absorbing CDDP for breast cancer in MM4 mouse, and the effect was satisfactory. Koyama [17] applied it to treat bile duct cancer of porta hepatis and its metastasis with the result that the tumor reduced and jaundice lightened for refractory porta hepatis hilar bile duct cancer of rabbit. Kabayashi[18] applied activated carbon absorbing MMC to inject submucously around gastric cancer for medicinal lymph node dissection (MLD). The MLD group containing 47 patients with gastric cancer was compared with another group of 125 patients only undergoing standard surgical treatment, and the survival time of the former was significantly longer than the latter.

In the recent years, scholars have developed lymphoimmunity chemotherapy by combining chemotherapy drugs with immune agents. Korovin[19] performed adjuvant therapy of lymphatic vessel perfusion for which dacarbasin and dacarbasin plus interferon were applied respectively for 1128 patients with melanoma of the skin. Five–year survival rate of lymphoimmunity chemotherapy group was 15.4% which was higher than 11.4% of single lymphatic chemotherapy group. The development of this research adds new contents to lymphatic chemotherapy.

In summary, lymphatic chemotherapy may effectively deliver chemotherapy drugs to lymphatic tissue, the local drug concentration is high, the duration is long, and the amount of drug components entering bloodstream is little which reduces general adverse effects. So it is a optimal chemo–therapy mode. At present, the research is preclinical or clinical probation stage and new dosage form is the research direction which should be used economically, conveniently and could be combined to apply. Convincingly, with the development and exploitation of more effective chemotherapy drugs, the prospect of lymphatic chemotherapy will become more expansive.

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