Lymphotaxis After Regional Chemotherapy with Carboplatin Bound to Activated Carbon on Patients with Breast Cancer

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Abstract **Objective** To investigate the lymphotaxis of carboplatin–activated carbon suspension (CP–CH) after administered to patients with breast cancer. **Methods** 32 patients with breast cancer were divided into 2 groups randomly (16/group). One group received regional subcutaneous injection of CP–CH adjacent to the primary tumor, another group received carboplatin solution (CP–Sol) under same condition. Modified radical mammectomy was executed 1, 12, 24, 72 hours later. Platinum concentrations in axillary lymph nodes were measured by Zeeman atomic absorption spectrometry (AAS). **Results** At 1, 12, 24, 72 hours after injection of CP–CH, the mean carboplatin concentration in lymph nodes was 11.23±5.66μg/g, 26.40± 11.18μg/g, 18.72±7.14μg/g, 15.44±6.92μg/g, respectively. At 1, 12, 24 hours after injection of CP–Sol, the carboplatin concentration was 0.24±0.06μg/g, 0.13±0.08μg/g, 0.12±0.04μg/g, respectively. No carboplatin was found at 72 hours after injection. Differences between the two groups were very significant in each corresponding comparison (P<0.01). **Conclusions** Regional administration of CP–CH to patients with breast cancer showed satisfactory character in delivering drug specifically and continuously to regional lymph nodes. The drug concentration in axillary lymph nodes was improved markedly.

Key Words breast cancer; drug therapy; carboplatin; activated carbon

During the past few years, many investigators have carried out researches into the regional chemotherapy targeting lymphatic tissues[1–4]. In the process, activated carbon has been applied frequently. Activated carbon particles have numerous micropores that could adsorb large amounts of anticancer agents, such as mitomycin C, methotrexate, peplomycin, or carboplatin. Once injected into the connective system, carbon particles are taken up selectively by lymphatic vessels and delivered to neighboring lymph nodes. To investigate the feasibility of using activated carbon in breast carcinoma, we contrived a prospective randomized control study and determined the drug concentration in axillary lymph nodes at different intervals following local administration of carboplatin bound to activated carbon on patients with breast cancer.

MATERIALS AND METHODS

Patients and study design

From June 2002 to March 2003, a total of 32 female patients with breast carcinoma proved by preoperative puncture biopsy were enrolled in this study. Ages of patients ranged from 32 to 61 years old (mean 48.6 years). The pathologic diagnoses consisted of ductal(n=16), lobular (n=13), medullary (n=2), and mucinous (n=1) carcinoma. Locations of primary tumors were outer–upper (n=19), outer–lower (n=4), inner–upper (n=6), and inner–lower (n=3). The inclusion criteria included: World Health Organization status of 0 or 1, without receiving chemotherapy or radiation therapy before, WBC count more than 4,000/μl and platelet count more than 100,000/μl, no abnormality of cardiac, renal, or liver functions. The patients who met these criteria were divided into 2 groups according to a prospectively generated randomization schedule, with 16 patients in each group, to receive the regional administration of either carboplatin–activated carbon suspension (CP–CH) or carboplatin solution (CP–Sol) as preoperative adjuvant treatment. Informed consent was obtained from each patient before enrollment.

Preparation of CP–CH

Activated carbon granules CHR–30 were ground by a ball–mill and sifted with a 100–mesh sieve. The fraction passing 100–mesh, 81% of which was smaller than 40μm, was used for this preparation as activated carbon particles. After the moisture was removed from the activated carbon particles by dry

heating at 120℃ for 2 hours, 375 mg of activated carbon particles were sealed in a glass tube. The glass tube containing activated carbon particles was sterilized under 2 atmospheres of pressure for 10 minutes and stored in a refrigerator. Prior to use, 100 mg of carboplatin dissolved in 20 ml normal saline was added to the activated carbon particles. The mixture was shaken for 10 minutes to allow adsorption of carboplatin onto the activated carbon particles. CP–CH was thus prepared[5].

Tissue platinum determinations

After biopsy proven, one group received subcutaneous injection of 4 ml CP–CH (containing 20 mg carboplatin), adjacent to the primary tumor. Another group received 4 ml CP–Sol containing 20 mg carboplatin in the same way. Modified radical mammectomy was performed 1, 12, 24, 72 hours later, respectively, with 4 patients at a time in each group. After axillary lymph nodes were excised entirely, 1–2 nodes were collected randomly to examination. Tissues were dissected to 200 mg accurately and placed into 5 ml screw cap tubes. Tissues were left to stand overnight with 4 ml of 10% hydrochloric acid and 70% nitric acid in proportion as 1: 4. The next day, tissues were digested for 2 hours at 90℃ in an electric frying pan positioned in a fume hood. The solubilized tissues were dried and jumbled with 0.5 ml Milli–Q water. Solutions were introduced into graphite furnace Zeeman atomic absorption spectrometry (AAS). Platinum analysis was undertaken as previously described[6]. The concentration of carboplatin equals to the concentration of platinum multiplied by 1.903.

Statistical analysis

Data are represented as the mean±SD. Results were tested for significant differences by Student´s t test and $P<0.05$ was considered as statistical significante.

RESULTS

At 1, 12, 24, 72 hours after injecting CP–CH, the mean carboplatin concentration in axillary lymph nodes was 11.23±5.66μg/g, 26.40±11.18μg/g, 18.72±7.14μg/g, 15.44±6.92μg/g, respectively. The carboplatin concentration was 0.24±0.06μg/g, 0.13±0.08μg/g, 0.12±0.04μg/g, respectively, at 1, 12, 24 hours after injecting CP–Sol. No carboplatin was found at 72 hours after injection of CP–Sol (Fig.1). Differences between the two groups were very significant in each corresponding comparison ($P<0.01$).

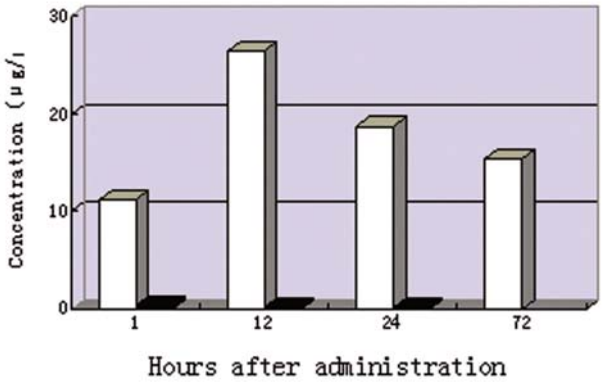

Fig.1 Carboplatin concentrations in axillary lymph nodes at different hours following administration. Open bars represent the mean carboplatin concentrations after administration of CP–CH. Closed bars represent the mean carboplatin concentrations after administration of CP–Sol.

DISCUSSION

In advanced breast carcinoma, regional lymphatic tissue adjacent to the primary tumor is the most common and important path for local metastasis, which are apt to bring on recurrence and distant metastases after radical resection. Effectively eradicating tumor cells which probably exist in regional lymphatic tissues is invaluable to prevent recurrence and metastasis. To achieve the goal, axillary lymph nodes are routinely removed during radical mammectomy. However, there are several paths for lymph drainage from breast to adjacent tissues. Lymph nodes in mediastinum, parasternum, porta hepatis, or abdomen are likely to be affected by accepting the lymph drained from breast. Unfortunately, they can hardly be resected during radical mammectomy. Similar problem can also be found in digestive tract cancers, which tend to metastasize lymphatically too. In recent years, some investigators have administered preoperative chemotherapy targeting regional lymph nodes on gastric, esophageal, rectal, or peritoneal cancer by using special drug carriers such as activated carbon or liposome [1–4]. Their results showed some promise of preventing metastasis and recurrence after radical resection.

In literatures published, activated carbon particles

were frequently used as a vehicle to transfer anticancer drugs[1-3]. Numerous micropores in activated carbon particles could adsorb large amounts of anticancer agents. To assess the feasibility of using activated carbon in breast carcinoma, we prepared CP-CH and determined carboplatin concentrations in axillary lymph nodes at different intervals following local administration of CP-CH. Under same condition, carboplatin concentrations after administration of CP-Sol were determined too. The results revealed that subcutaneous injection of CP-CH delivered much more carboplatin to the regional lymph nodes, as compared with the equivalent dose of CP-Sol. Carboplatin bound to activated carbon particles has the advantages of targeting regional lymphatic tissues and of being released slowly and locally at high concentrations, which would be helpful to improve anticancer efficacy.

In summary, our study demonstrated that subcutaneous injection of CP-CH adjacent to the primary tumor is suitable for specific and efficient delivery of carboplatin to the regional lymph nodes, which are susceptible to metastasis. Preoperative chemotherapy targeting the regional lymph nodes appears to be an effective method of preventing recurrence and improving survival after radical mammectomy.

REFERENCES

1. Huang Y, Hagiwara A, Wang W, et al. Local injection of M-CH combined with i. p. hyperthermic hypo-osmolar infusion is an effective therapy in advanced gastric cancer. Anticancer Drugs, 2002, 13:431-435.
2. Kin S, Nakase Y, Fukuda K, et al. Endoscopic local injection of anticancer drugs bound to carbon particles for treatment of advanced rectal cancer, when surgical treatment was contraindicated. Gan To Kagaku Ryoho, 2002, 29: 2413-2415.
3. Hagiwara A, Takahashi T, Sawai K, et al. Lymph nodal vital staining with newer carbon particle suspensions compared with india ink. Lymphology, 1992, 25:84-88.
4. Akomo Y, Mizuno I, Yotsuyanagi T, et al. Chemotherapy targeting regional lymph nodes by gastric submucosal injection of liposomal adriamycin in patients with gastric carcinoma. Jpn J Cancer Res, 1994, 85:652-658.
5. Takahashi T, Hagiwara A, Shimotsuma M, et al. Prophylaxis and treatment of peritoneal carcinomatosis: intraperitoneal chemotherapy with mitomycin C bound to activated carbon particles. World J surg, 1995, 19: 565-569.
6. Meerum-Terwogt JM, Tibben MM, Welbank H, et al. Validated method for the determination of platinum from a liposomal source (SPI-77) in human plasma using graphite furnace Zeeman atomic absorption spectrometry. Fresenius J Anal Chem, 2000, 366:298-302.