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Short report

A pilot study of fiberscopy-guided local injection of anti-cancer drugs bound to carbon particles for control of rectal cancer

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Rectal cancer patients with contra-indicatory risks may not be able to undergo surgery. In these cases the preferred treatment is chemotherapy. The present dosage formulation, consisting of an anti-cancer drug bound to activated carbon particles, was designed to deliver the anti-cancer drug at high concentration selectively to the injection site as well as to the regional lymph nodes and to improve survival of mice bearing cancer with nodal metastases, as compared to the same dose of aqueous anti-cancer drug in animal experiments. The present clinical trial includes two patients with histologically confirmed adenocarcinoma of the rectum and who had risks contra-indicating surgery. Carbon particles adsorbing anti-cancer drugs totaling 400 mg of methotrexate and 32 mg of mitomycin C in one patient and 100 mg of methotrexate and 8 mg of mitomycin C in another patient were injected into the cancer tissue under guidance of a colono-fiberscope. The rectal cancers were successfully reduced in size and controlled over 2 years or 6 months until the patients died from other causes. Side effect was mild. Local injection of this dosage formulation will be useful for the control of rectal cancer in patients who cannot undergo surgery. [© 1998 Lippincott-Raven Publishers.]

Key words: Activated carbon particles, ameliorative therapy, anti-cancer drugs, rectal cancer.

Introduction

Rectal cancer patients with contra-indicatory risks may not be able to undergo surgery. In these cases, one of the preferred therapies is anti-cancer chemotherapy. Locally injected water-soluble small molecules, which include most anti-cancer drugs, are absorbed rapidly from the injection site into the circulation and do not remain concentrated selectively for any significant period of time at the injection site.[1] Thus, it is difficult to control the tumors with local injection of aqueous anti-cancer drugs. In contrast, small particles such as activated carbon particles are retained at the injection site and absorbed gradually into the regional lymph nodes.[2] Utilizing this difference between the absorption of aqueous solutions and small particles, we have developed another dosage formulation which is composed of anti-cancer drug bound to fine activated carbon particles.[3] Animal experiments revealed that this dosage formulation maintained higher levels of the anti-cancer drug in the injection site as well as in the regional lymph nodes than did the equivalent dose of aqueous anti-cancer drug.[3] The present paper reports a pilot clinical trial, in which local injection of anti-cancer drugs bound to carbon particles successfully ameliorated rectal cancer in two patients who could not receive surgery due to contra-indicatory risks.

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Methods and results

Preparation of the dosage formulation

The dosage formulation consisting of anti-cancer drug bound to carbon particles was prepared as reported previously.[3] Activated carbon particles (AC-1500, specially prepared in our laboratory), which are similar to Activated Carbon 1500AA® produced by Mitsubishi Chemicals (Tokyo, Japan),[4] have an average diameter of 20 nm. The adsorption isotherm of the activated carbon for methotrexate (MTX) in saline at 37°C was determined as $Q=270C^{0.16}$, where Q is the amount of MTX which is adsorbed onto the activated carbon in μg/mg and C is the concentration of free MTX in μg/ml. Activated carbon at 50 mg/ml and polyvinylpyrrolidone (PVP K-30®; Nakalai Chemicals, Kyoto, Japan) at 30 mg/ml were

mixed in physiological saline and kneaded with rollers to produce a suspension with an average particle diameter of 167 nm.[4] MTX (methotrexate sodium Parenteral®; Lederle Laboratories Division,

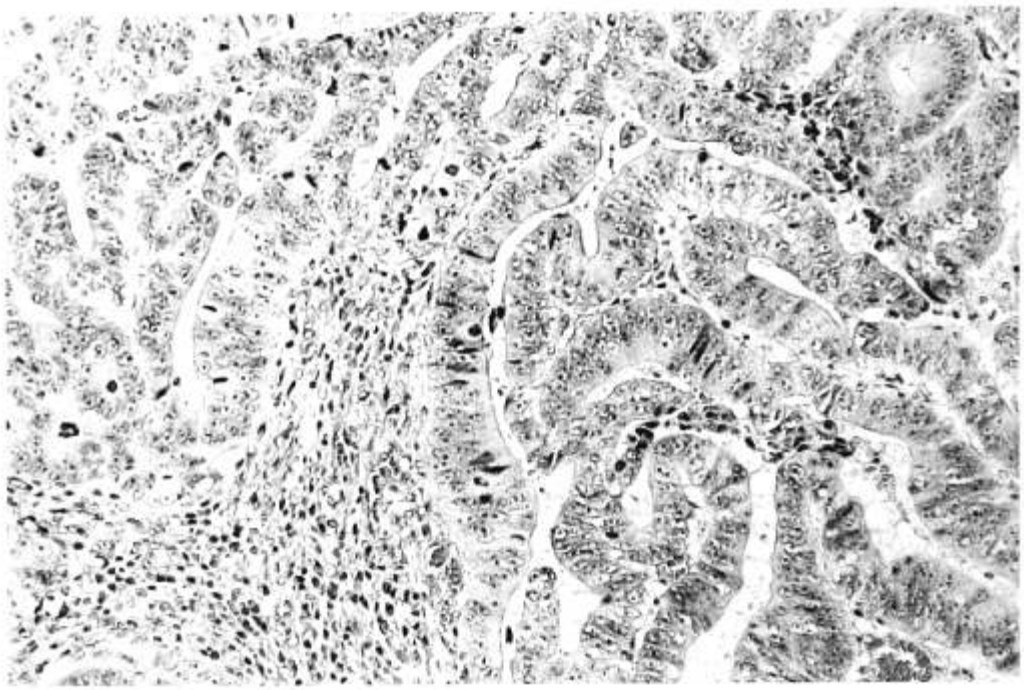

Figure 1. Biopsy specimen in case 1. Microscopically well-differentiated adenocarcinoma was revealed in the biopsy specimen taken from the rectal tumor in case 1. (Hematoxylin & eosin, magnification of ×100.)

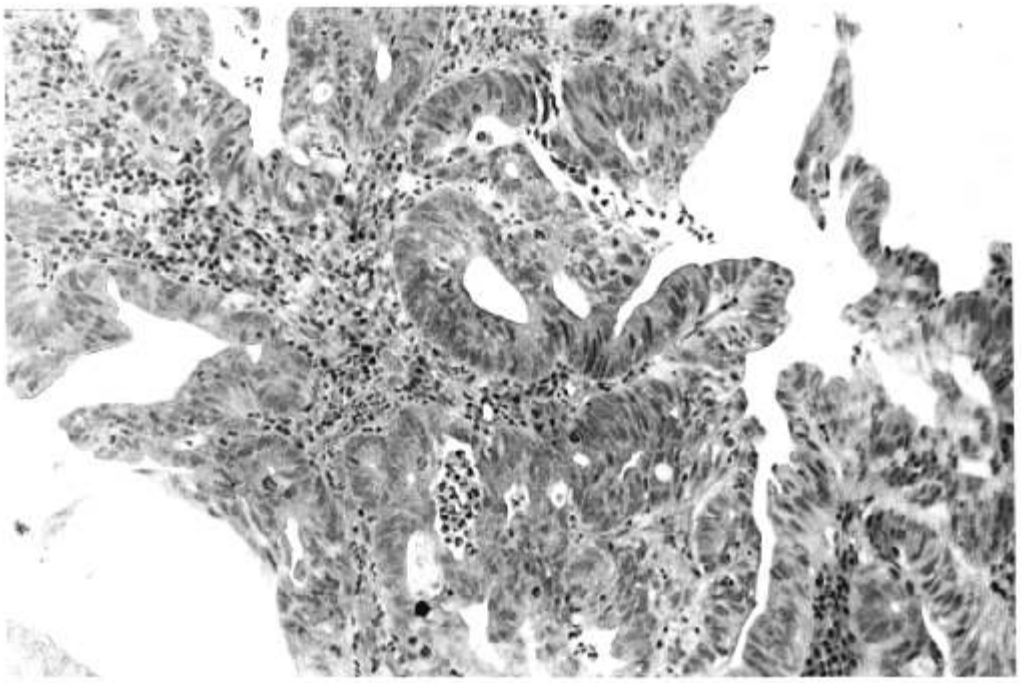

Figure 3. Biopsy specimen in case 2. Microscopically well-differentiated adenocarcinoma was revealed in the biopsy specimen taken from the rectal tumor in case 2. (Hematoxylin & eosin, magnification of ×100.)

American Cyanamid, Pearl River, NY) was added to the activated carbon suspension at a concentration of 25 mg/ml. This mixture was shaken for 6 h so that the MTX was adsorbed onto the activated carbon particles, resulting in a new formulation (MTX-CH). In MTX-CH, 24,951 μg/ml of MTX is adsorbed onto the activated carbon and only 49 μg/ml remains free. Using similar procedures, we prepared MMC-CH which consists of 500–571 μg/ml of mitomycin C (MMC, Mitomycin S Kyowa®; Kyowa Hakko Kogyo, Tokyo, Japan), 50 mg/ml of activated carbon (Carbon #40®; Mitsubishi Chemicals, Tokyo, Japan) and 20 mg/ml of polyvinylpyrrolidone in saline. In MMC-CH, 1.0–1.5 μg/ml of MMC was in an unbound state while the remaining MMC was adsorbed onto the activated carbon.

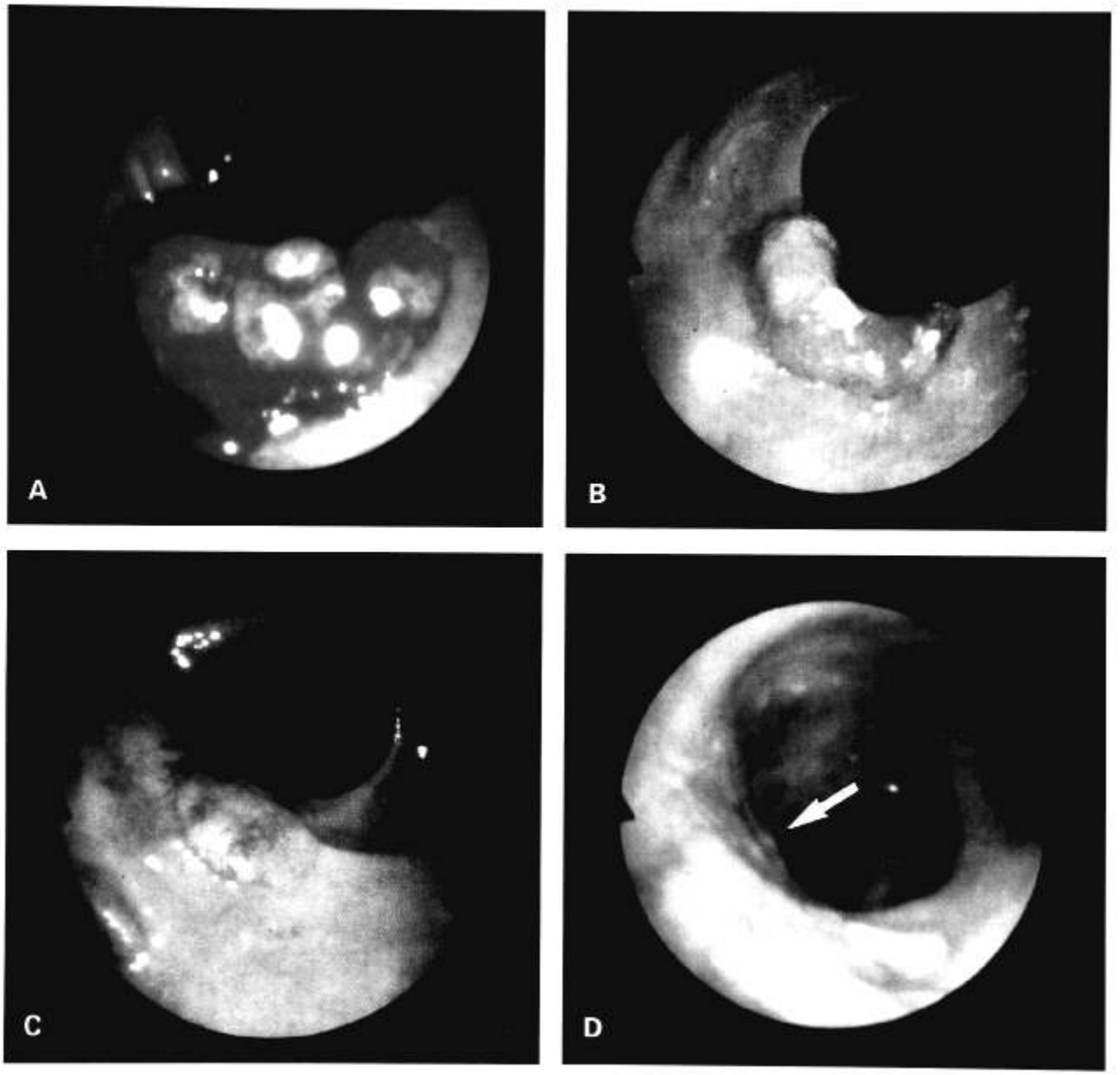

Figure 2. Colono-fiberscopic view of rectal cancer. (A) Before drug injection, there is a cancerous lesion from which significant bleeding occurs. (B) After the first course of drug injection, the cancerous lesion has become small and the bleeding stops. (C) After the second course of the drug injection, the cancerous lesion has become smaller. (D) After the fourth course of drug injection, the cancerous lesion has disappeared and erosive mucosa is seen at the site where the cancerous tumor was located previously (arrow).

Therapeutic methods and results

We selected protruded type carcinomas in which any change of size is easily evaluated. Two patients with adenocarcinoma of the rectum, as diagnosed by barium X-ray examination and colono-fiberscopy with biopsy and confirmed histologically, were included in this trial. These two patients could not receive surgery because of pulmonary or cardiac disease, which was considered to be a severe risk contra-indicating surgery. MTX-CH and MMC-CH were injected into the rectal cancer. During one course of treatment, MTX-CH at an MTX dose of 50 mg was injected into the primary tumor on each of days 1 and 15, and MMC-CH at an MMC dose of 4 mg was injected on each of days 8 and 22, guided by a colono-fiberscope through an endoscopic injector (NM-III K injector; Olympus Optical, Tokyo, Japan). If necessary, further similar courses were administered. Follow-up consisted of colono-fiberscopy at intervals of less than 3 months, until the death of the patients. Other anti-cancer treatments were not administered. Both patients gave informed consent and the department gave ethical approval for the present trial.

Case 1

A 75-year-old male patient was diagnosed with well-differentiated adenocarcinoma (Figure 1) of the rectum by colono-fiberscopy with biopsy. Remarkable and uncontrolled bleeding from the tumor was observed (Figure 2A). This patient had chronic obstructive and restrictive pulmonary disease due to an old pulmonary tuberculosis and bronchoectasia which constituted a severe risk for surgery. A first course of treatment consisting of 50 mg MTX × two times and 4 mg MMC × two times was administered in the form of anti-cancer drug bound to carbon particles injected into the rectal cancer tissues under guidance of a colono-fiberscope through an endoscopic injector. Following this treatment the tumor decreased in size and the bleeding stopped (Figure 2B). After the second course of drug injection therapy administered similarly 2 months later, the lesion became much smaller (Figure 2C). The treatment regimen was repeated a further two times at intervals of 4 and 6 months, and the cancer was well controlled (Figure 2D) for 2 years until the patient died from pneumonia. Although a fever of 38°C was found as a side effect following the first administration, no other side effects were noted.

Figure 4. Barium enema X-ray film in case 2. (Left) Before drug therapy, cancerous lesion (arrow) can be detected. (Right) After drug therapy, the cancerous lesion has become small (arrow).

Case 2

A 77-year-old female patient who had complained of anal hemorrhage and sense of residual feces on and after defecation was diagnosed to have a well-differentiated adenocarcinoma (Figure 3) of the rectum by colono-fiberscopy with biopsy and bariumenema X-ray film (Figure 4, left). She had cardiac disease that presented a severe risk for surgery. Only one course of the treatment regimen consisting of 50 mg MTX × two times and 4 mg MMC × two times was administered. Following this treatment, the tumor became small (Figure 4, right) and the complaints were improved markedly. The tumor was well controlled for 6 months until the patient died from cardiac disease. No side effects were noted.

Discussion

In this dosage formulation, there is a dynamic equilibrium between the adsorbed and free drug. When the concentration of the drug decreases around the activated carbon particle, the activated carbon releases some of the adsorbed drug, elevating the free drug concentration. Thus, the concentration of the free drug is maintained at a constant level. The adsorption isotherm shows that the adsorbency of the activated carbon is very high. This means that the activated carbon maintains the free drug concentration at a fixed level for an extended period of time around the activated carbon. This property of the present dosage formulation yields higher levels of the anti-cancer drug for long periods of time at the injection site as well as in the regional lymph nodes than did the equivalent dose of aqueous anti-cancer drug, as revealed by animal experiments.[3]

When patients with rectal cancer cannot undergo surgery due to some operative risk, radiation is another preferred therapy. Although radiation can control rectal cancer, it is costly and requires specialized instruments. On the contrary, local injection of the present dosage formulation is cheap and requires only a fiberscope. Although the present trial includes only two cases and further study will be necessary, the present results suggest that fiberscopy-guided local injection of anti-cancer drugs bound to fine activated carbon particles will become another useful therapy for ameliorating and controlling the protruding type of rectal cancer in patients who cannot undergo surgery due to operative risks.

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