Therapeutic effects of 5-fluorouracil sustained-release particles in 81 malignant pericardial effusion patients

Yong-Li Ji, Rui-Zhi Li, Li-Fang Xue, Ping Li, Xiao-Hong Liang, Liang Dong, Yang Gao, Wen-Chao Cui, Min-Xia Pang*

Department of Ultrasonography, Shengli Oil Field Center Hospital, Dongying, Shandong Province, China

Received 16 June 2014; accepted 27 October 2014
Available online 20 December 2014

KEYWORDS
5-Fluorouracil sustained-release particles; Cardiac tangent direction; Malignant pericardial effusion; Pericardiocentesis; Ultrasonic interventional therapy

Abstract This study aimed to investigate the clinical application value of the 5-fluorouracil (5-FU) sustained-release particles implanted along the cardiac tangent direction into malignant pericardial effusion (MPCE). A total of 81 MPCE patients underwent pericardiocentesis, and were implanted with 5-FU sustained-release particles into the pericardial cavity under ultrasound guidance. The puncturing path was along the cardiac tangent direction. Ultrasound examinations were performed every week, and the efficacy was evaluated 4 weeks after treatment. The 45 patients who were treated with pericardial catheter drainage and simultaneous intracavitary chemotherapy were used as the control group. The success rate of pericardiocentesis was 100%. Ultrasound reviews performed 4 weeks after treatment showed that 71 cases achieved complete remission and eight cases achieved partial remission, while treatment was completely ineffective in two cases. The total remission rate was 97.53%, which was significantly higher than that of the control group (77.78%, p < 0.01). The implantation of 5-FU sustained-release particles along the cardiac tangent direction was safe, and demonstrated good efficacy and fewer adverse reactions. Thus, this method could be ideal for the treatment of MPCE.

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Introduction

Malignant pericardial effusion (MPCE) is a common clinical manifestation in patients with advanced malignant cancers that seriously affect the prognosis. The effective control of pericardial effusion is significant at alleviating the suffering of patients and prolonging their lives. Pericardiocentesis, accompanied with catheter drainage (CD) and intracavitary chemotherapy, is the main treatment method for MPCE. In recent years, China has independently developed implantable sustained-release fluorouracil, which has been applied for the treatment of various malignant tumors or prevention of metastasis and recurrence, and achieved certain positive effects [1,2]. Many scholars have applied this method during surgery for various gastrointestinal cancers [3]. Some scholars have also made useful attempts in the treatment of liver cancer [4], pancreatic cancer, breast cancer, and ovarian cancer [5]. Numerous studies have shown that 5-fluorouracil (5-FU) sustained-release implantation dose has good safety and efficacy in the treatment of malignant pleural effusions and malignant ascites, especially in palliative treatment [6]. As for its treatment, the currently widely-accepted strategy during the emergency was rapid pericardial puncture, fluid-drainage-decompression and saving lives, and the regeneration of the effusion should be controlled or suppressed, which is the current clinical research hotspot. In this study, 5-FU particles instead of other chemotherapeutic drugs were imported into pericardial cavity by ultrasonic intervention technology to treat MPCE. This method is a novel exploration in the ultrasonic intervention field. In this study, a particle implantation (PI) needle was used to pierce through the skin and into the pericardial cavity, completing the processes of pumping fluid and implanting medicine. The pericardium was decompressed, and etiological treatment was simultaneously performed, which achieved good results. A preliminary summary regarding the treatment of 81 cases of MPCE patients is reported in this paper.

Patients and methods

Case selection

A total of 81 hospitalized patients (PI group: comprised 33 males and 48 females, mean age, 61 years), suffering from pericardial metastasis of late malignant tumors and different levels of pericardial effusion, were selected from the Shengli Oil Field Center Hospital from October 2006 to October 2011. The KPS scores of the PI group ranged from 20 points to 50 points, with an expected survival duration > 2 months. The primary tumors were pathologically confirmed, included 44 cases of lung cancer, 11 cases of breast cancer, 11 cases of gastrointestinal cancer, six cases of ovarian and cervical cancer, and nine cases of other malignancies. The selected cases suffered from a large or very large surrounding pericardial effusion, in which the width of the nonecho region was 2.0–6.0 cm, and accompanied with a swinging heart. Eight cases exhibited pericardial metastases or irregular thickening of the parietal pericardium (Fig. 1), and 73 cases exhibited pleural effusion (90%).

Figure 1. The metastatic lesion can be seen in the pericardium.

A total of 45 patients (25 males and 20 females with an average age of 59 years old) underwent pericardial CD and intracavitary chemotherapy during the same period, and they were established as the controls (CD group). Among these 45 cases, 23 were of lung cancer, nine were of breast cancer, six were of gastrointestinal cancer, one was of ovarian cancer, and six were of other malignancies. All the CD patients had large or extremely large surrounding pericardial effusion.

Equipment

A DU8 and DU6 color Doppler ultrasonic diagnostic apparatus (Esaote Group Co., Genoa, Italy), with a convex array probe (2.5–7.0 MHz) and/or linear array probe (5.0–10 MHz), was used as the intervention monitoring and guiding device. An angle-fixed side-type titanium guiding device, which was provided by the ultrasound machine manufacturer (angles of 20°, 25°, 30°, 35°, and 45°), was used as the puncturing guide. An 18-gauge particle-implantation (PI) dedicated needle (outer diameter 1.2 mm, internal diameter 1.0 mm) was used in the apparatus.

Drugs

The drugs used were sustained-release 5-FU (Wuhu Zhong-ren Pharmaceutical Co., Ltd., Wuhu, China), which has the trade name of Sinofuan (Approval No: H20030345). This drug is a long-term antitumor formulation, and appear as a milk-white cylinder-like particle. The diameter of each particle is 0.8 mm, length 4 mm. Each particle contains approximately 2 mg of 5-FU, and 100 mg for each unit. The releasing period ranges from 15 days to 20 days [7].

Puncturing path

To improve the safety of paracentesis, the cardiac tangent or approximately tangent direction was established as the puncturing path (denoted as the cardiac tangent direction) under real-time ultrasonic guidance, which would avoid the possibility of heart damage.

The puncturing point was preoperatively located at the place where the pericardial effusion volume was relatively...
The guiding line function of the ultrasonic instrument was used in determining the right puncturing path to ensure that the puncturing path maintained the tangent or approximately tangent direction towards the heart in this region (Fig. 2). The puncturing angle \(20^\circ-45^\circ\) was then fixed, and the puncturing point marked on the body skin surface.

**Preoperative preparation**

Before puncturing, the patient’s medical history should be learned to determine the cause of pericardial effusion. Moreover, the patient should not have recently consumed anticoagulant drugs and not have undergone hemodialysis, to avoid uncontrollable bleeding after puncture. Preoperative examinations of blood pressure, electrocardiogram must be performed, blood routine, and blood coagulation must also be performed to confirm the platelet count and clotting time of the patient. Communication should be carried out with patients and their families preoperatively to explain the disease and inform the risks for informed consent. Preoperative ultrasound examination should be performed to understand the patient’s general condition, and assess the extent of pericardial effusion. During the surgery, the clinician should accompany the patient during the entire period, and establish intravenous access. Moreover, the clinician should prepare the necessary rescue medications, cardiac defibrillator, and other rescue equipment to correct unexpected situations.

**Procedure**

The patient was asked to lie in the supine, semirecumbent, or sitting position. Then, 2% lidocaine was injected for local anesthesia. The 18-gauge PI needle was punctured along the guiding line on an ultrasonic wave display screen using the Seldinger technique. When the parietal pericardium was pierced, the needlepoint, which displayed the *equal echo status*, was in the dark area of the pericardial liquid. The needle body then continued to advance by 2.0–3.0 cm. The fluid could be seen when the needle core was pulled out. Subsequently, the needle handle was rapidly connected with the extension tube for slow drainage. The amount of the first drainage was determined by the pericardial pressure, and was usually 100 mL. This amount was limited by the balance of intrapericardial pressure and atmospheric pressure to avoid the negative suction pressure state. After drainage, the pericardial cavity pressure was observed immediately. If the inside and outside pericardial pressures were equal, the 5-FU sustained-release chemotherapy particles could be implanted. The extension tube was removed, and 400 mg of 5-FU sustained-release particles was implanted into the pericardial cavity. After implantation, a secondary drainage was performed (Fig. 3), which was stopped when the remaining amount of effusion was about 20–25% of the total amount. After completing the surgery, the needle was removed. Then, the opening was sealed with sterile dressing.

**Efficacy evaluation**

No uniform international standard towards the efficacy evaluation of MPCE currently exists. Based on the tumor efficacy evaluation criteria and RECIST (2000) evaluation of the nontarget lesions by the World Health Organisation [8], the efficacy was evaluated according to the following criteria after treatment: (1) complete remission (CR), in which pericardial effusion completely disappeared or left trace remnants, and the clinical symptoms were significantly relieved and maintained for \(>30\) days; (2) partial remission (PR), in which pericardial effusion was reduced by \(>50\)%, and the clinical symptoms and signs were partially remitted and maintained for \(>30\) days; and (3) no response, in which the situation did not meet the above criteria, and the pericardial tamponade symptoms achieved no relief or increased. The total efficiency was calculated using the following formula: total efficiency = \((\text{CR number} + \text{PR number})/\text{total number of cases} \times 100\%\).

After the treatment, ultrasound examination was performed once every 5–7 days to observe the changes in pericardial effusion. Other treatments were performed in the invalid or progressed patients, whereas the patients

![Figure 2. Image of the puncturing along the cardiac tangent.](image)

![Figure 3. Puncturing was carried out along the approximate tangent direction of the pericardial effusion, partial liquid was extracted, 5-fluorouracil sustained-release particle was implanted, and then 600 mL liquid was extracted again.](image)
with obvious effects continued to be observed. Ultrasound examination was performed for the efficacy evaluation 4 weeks after treatment.

Statistical analysis

SPSS 13.0 was used for statistical analysis, and intergroup comparisons were made using χ² test. A p-value < 0.05 was set as statistical significance.

Results

Puncturing results

All 81 cases underwent puncturing successfully the first time. Among these cases, 69 had bloody effusion (85.19%), whereas 12 had pale yellow or yellow effusion (14.81%). After the effusion was centrifuged, 57 cases were found positive for tumor cells (70.37%). The total drainage volume was 300–1500 mL before and after drug implantation, and the average volume was approximately 900 mL.

Short-term efficacy evaluation

The postoperative 1st week ultrasound results show no growth in the residual fluid volume after drainage in all cases. The postoperative 2nd week ultrasound results show that 71 cases exhibited a significant reduction in the residual liquid (liquid width was 5–10 mm), eight cases exhibited slight decrease in the residual liquid (liquid width was 10–15 mm) and two cases showed no significant changes in the residual liquid. The postoperative 3rd week ultrasound results show that 71 cases exhibited a significant reduction in residual fluid compared to the 2nd week. Among these 71 cases, 45 cases exhibited the complete disappearance of residual liquid (Fig. 4), whereas 26 still exhibited trace or small amounts of fluid (liquid width was 4–8 mm). The amount of residual liquid of the other eight cases continued to decrease (liquid width was 8–12 mm), whereas no noticeable change was observed in the amount of residual liquid in the other two cases.

According to established clinical evaluation criteria, an ultrasound examination was performed on the postoperative 4th week to evaluate the short-term effects. The 71 cases in which residual effusion completely disappeared or only trace fluid remained were identified as CR. Eight cases were identified as PR because their effusion decreased, but little or moderate amount of fluid still remained. Two cases were identified as no response because no postoperative reduction of effusion was observed. In these two cases, one patient had renal carcinoma, and the other had high-position cholangiocarcinoma. These two patients were given pericardial CD.

Efficacy comparison

The total effective rate of MPCE PI therapy was 97.53%, which was higher than CD (77.78%), with p < 0.01 (Table 1).

Adverse reactions

Three patients complained of palpitation and chest tightness on the day after the surgery, with a pulse > 120 beats/min. These symptoms improved after oxygen inhalation and oral administration of metoprolol. Shock or fever did not occur in any of the cases.

Discussion

MPCE is a common complication in patients with advanced cancers, and about one-third of MPCE patients eventually die because of clinical cardiac tamponade. MPCE is often bloody, has a large volume and fast growth speed and is difficult to control. Early diagnosis and treatment can significantly improve the symptoms, and provide opportunities for the next step of treatment. The current clinical approach commonly used is based on minimally invasive intervention, such as pericardial paracentesis or CD, than local methods, such as cavity medication (including biological immunosuppressive agents, herbal preparations, chemotherapy drugs, hardening agent, and targeting agents) and cavity hyperthermia.

The method of pericardiocentesis for CD, combined with intracavitary local chemotherapy or chemotherapy + biological response modifier, has been applied for many years. The drugs injected include drugs with relatively small cardiotoxicity, such as cisplatin, carboplatin, 5-FU and mitomycin. Research [8] has shown that pericardiocentesis for CD, plus intracavitary local chemotherapy, can reduce the systemic side effects with high efficacy compared with intravenous chemotherapy. This method can greatly improve the body’s tolerance against anticancer drugs, and the body’s immune function is less affected. However, given the efficacy of chemotherapy drugs, the aqueous dosage form can only be maintained for several hours, and the use of a catheter may be inconvenient. Thus, the clinical application of this method is limited to some degree.
The 5-FU sustained-release chemotherapy particle, which is currently the most widely used clinical sustained-release agent, is made of antipyrimidine drugs, and has dual characteristics of sustained-release and targeting. In the pericardial cavity, this method can maintain the effective concentration of drugs for a long period to enhance the anticancer effects, and does not result in serious adverse reactions. During the implantation procedure and postoperative ultrasound in this study, 5-FU sustained-release particles floated in the effusion, and exhibited a state of motion caused by the heartbeat. The implanted particles gathered locally, and the efficacy was unaffected because of the postural changes. The 5-FU dose used in the previous intracavitary chemotherapy was also used in this study, and 400 mg of sustained-release particles containing the appropriate content of 5-FU were selected and implanted into the pericardium. This method achieved good results with total efficiency of 97.53% and CR rate of 87.65%, which were significantly higher than those of CD ($p < 0.01$).

Pericardiocentesis combined with implantation of a sustained-release chemotherapeutic agent is a new exploration in interventional therapy. Three puncturing sites and paths are generally used. In the xiphoid process-inferior path, the puncturing site is 1 cm below the cross of the left costal margin and left edge of xiphoid process. The puncture needle is 30–45° against the abdominal wall, with the tip pointing to the left nipple, and the puncturing depth is about 4.0–6.0 cm. In the second path, the puncturing site is 2.0 cm from the fourth rib to the left sternal border. The needle is perpendicular to the chest wall, and the puncturing depth is 2.0–4.0 cm. The path is equivalent to the bare area of the pericardium. In the third path, the puncturing site is 2.0 cm inside the cardiac dullness of the left fourth intercostal space. The needle is pointed backwards, and the inner direction is pointed to the spine. The puncturing depth is 2.0–4.0 cm. By contrast, pericardiocentesis performed in the bare area of the pericardium is the safest site because the fibrous pericardium is directly stuck to the chest wall [9], vertical puncturing does not affect the pleural cavity and puncturing distance is the shortest. However, pericardiocentesis in this site has smaller choice space. Moreover, this site is often not considered in elderly patients because of the narrow intercostal space, and puncturing needs to be vertical or nearly vertical against the chest wall. Furthermore, the heart wall and coronary artery may be injured with fluid reduction when draining effusion. The aforementioned three puncturing paths are suitable when the heart does not exhibit shifting, and no resistance/obstacle exists between the chest wall and intercostal space. However, in real clinical situations, special cases are often encountered, such as the pulling and shifting of the heart of lung resection patients to the operation side. Such cases have a greater risk in puncturing the pericardium based on the conventional path. If a tumor invades the ribs after rib resection surgery, the titanium plate would be implanted into the rib-absent area, and the conventional route for pericardiocentesis would be inappropriate.

This study attempted to perform pericardiocentesis along the cardiac tangent direction. The heart and pericardium constitute a morphological structure similar to an irregularly shaped cone or pear. Sternotomal scanning revealed that any of its cross-sections can be considered as arc or near-arc, particularly with a large or very large amount of pericardial effusion. Moreover, the separation width between the two splanchnic walls can increase, thick liquid can surround or wrap the epicardium surface, the amount of liquid in front of the heart is often more than that behind the heart and the widest region is often located in the apical point. With the increase in pericardial effusion, the arc of the ultrasonic cross-section would correspondingly increase, and create viable conditions for searching the heart tangent or approximate tangent direction. These ultrasonographic features of MPCE are the anatomical basis of establishing the heart tangent or nearly tangent direction as the pericardiocentesis path.

Pericardiocentesis through the heart tangent direction must have accurate ultrasound guidance. The direct view of ultrasound imaging clearly displays every step. In the process of draining, the heart walls and coronary arteries are unaffected even when effusion decreases.

The accurate puncturing site and path are highly important in pericardiocentesis through the heart tangent direction. Locating the heart tangent or approximate tangent direction and a suitable puncturing site are essential to successful puncturing. During the operation, several points should be noted. Firstly, probe selection should be flexible for the patients with the extended resection of left breast because the chest wall is thinner. A smaller convex or linear high-frequency probe can be used to reduce the blind spots and obtain clear guidance image. Secondly, the image should be appropriately enlarged when necessary to facilitate clear display of the tip. Thirdly, the image enhancement technology inside the machine should be applied, such as diamond imaging technology and harmonic technology, to obtain higher quality images for facilitating guidance. Fourthly, the needle body should be continuously moved forward by 2.0–3.0 cm when breaking through the pericardium, and the beating heart should not be stabbed when effusion draining reduces the pericardium separation width. Fifthly, draining should be slow because

<table>
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<tr>
<th>Grouping</th>
<th>Cases</th>
<th>CR</th>
<th>PR</th>
<th>NR</th>
<th>Total efficacy</th>
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<tr>
<td>PI</td>
<td>81</td>
<td>71 (87.65)</td>
<td>8 (9.88)</td>
<td>2 (2.47)</td>
<td>79 (97.53)</td>
</tr>
<tr>
<td>CD</td>
<td>45</td>
<td>19 (42.22)</td>
<td>16 (35.56)</td>
<td>10 (22.22)</td>
<td>35 (77.78)</td>
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$\chi^2$ test \[ \chi^2 = 10.91, p < 0.01 \]

CR = complete remission; NR = no response; PR = partial remission.
the heart tolerates high pressure from the pericardium. Heart failure or pulmonary edema would appear when pressure suddenly reduces. Sixthly, the sequence should be puncturing—draining—implanting—redraining. Pericardiocentesis should be performed along the cardiac tangent direction. Some effusion (60–100 mL) should be drained. When the pericardial inner pressure is close to the atmospheric pressure, the particles should be implanted. Then, secondary draining can be performed. Given that the particles are cylindrical, they spread with the beating heart after implantation, and are drained out with the effusion extraction.

In this study, the puncturing—draining—implanting—redraining mode was conducive to ultrasonic display, and could also reduce the toxicity of chemotherapy particles against the heart. The 5-FU sustained-release particles were implanted directly into the pericardial cavity, and the released 5-FU directly faced the surface of the heart. However, whether this process poses a threat to the safety of a patient remains unknown. Through follow-up of patients in the PI group, three patients exhibited palpitation and suffocation 1 day after surgery, and these symptoms improved after oxygen inhalation and oral administration of metoprolol. This result does not indicate that the patients were unsuitable for pericardial pressure after effusion draining, but could be attributed to the first release of 5-FU or the drug burst release-caused reaction. Burst release refers to the transient high-concentration drug release caused by the residual drugs among the particle microcapsule before the sustained-release formulation reaches a releasing plateau in the releasing medium or in vivo, which may lead to toxic drug levels in the body [10–12]. Studies have suggested that the preparation should undergo in vitro cleaning before entering the body. In this study, the puncturing—draining—implanting—redraining mode was equivalent to the in vitro cleaning medicine. Although no patient had severe cardiac toxicity, these results should be interpreted carefully. The longest follow-up period of the patients using this therapy reached 5 years, and no complications, such as pericardial adhesions, were found.

The 5-FU sustained-release PI therapy along the cardiac tangent direction for MPCE treatment is classified as ultrasound-guided intervention therapy, and is a novel attempt in the field of interventional ultrasound. The operation was simple, inexpensive, effective and reliable, and did not result in radiation damage. Given that a limited number of cases were included in this study, and the follow-up time was short, the long-term effects of this operation need further investigation.

Acknowledgments

This study was supported by Shandong Provincial Dongying Science & Technology Project (Dongkezi [2006]116-21); this research has achieved the 1st Price of Dongying Science & Technology Progress.

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