Video-assisted transcatheter lung perfusion regional chemotherapy

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Abstract

Objective: To establish a technique for performing isolated lung perfusion (ILP) under video-assisted thoracic surgery (VATS) to treat unresectable lung malignancies. Methods: Under fluoroscopic and thoracoscopic guidance, five canine left lungs were isolated by means of an endovascular technique comprising pulmonary artery cannulation through the right femoral vein and pulmonary vein cannulation through the left auricular appendage (VATS-ILP). ILP was performed for 20 min at a flow rate of 30 ml/min with a high-dose cisplatin solution (50 μg/ml). Toxicity and pharmacokinetics of VATS-ILP were compared with those of conventional ILP performed in five additional lungs. Results: VATS-ILP was performed safely without adverse reaction. Both VATS-ILP and conventional ILP delivered a high dose of cisplatin to the treated lung (total platinum concentration: 48 ± 17 μg/g tissue for VATS-ILP vs. 51 ± 19 μg/g tissue for conventional ILP, P > 0.1) without significant systemic leakage (total platinum concentration: 0.4 ± 0.1 μg/ml plasma vs. 0.5 ± 0.2 μg/ml plasma, P > 0.1). In addition, no significant differences were observed between the groups in the serum lactate dehydrogenase level, serum angiotensin-converting enzyme level, body weight change, or mid-term histological change following ILP. A significantly smaller thoracotomy was used for VATS-ILP than for conventional ILP (4.7 ± 0.4 cm for VATS-ILP vs. 12 ± 0.7 cm for conventional ILP, P < 0.001) because VATS-ILP required neither arteriotomy nor venotomy. Conclusions: We established a canine VATS-ILP model that showed pharmacokinetic potential similar to that of conventional ILP. A clinical trial of VATS-ILP with cytotoxic drugs is warranted.

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Keywords: Isolated lung perfusion; Video-assisted thoracic surgery; Cisplatin; Regional chemotherapy

1. Introduction

The lung is one of the most frequent sites of metastasis from all malignant tumors. For patients with metastatic lung disease, surgical resection remains the only potentially curative option, although the reported 5-year survival rates after complete metastasectomy are no more than 25-40% [1-3]. Systemic chemotherapy often results in a poor outcome due to dose-limiting systemic toxicity. Regional chemotherapy by means of isolated lung perfusion (ILP) was developed to deliver high-dose antitumor agents to the lung but limit systemic toxicity [4-6]. Several human trials were conducted to investigate the efficacy of ILP with dose-dependent cytotoxic drugs for treatment of lung metastases [7-9]. Unfortunately, ILP showed only limited antitumor potency, and only limited numbers of patients participated in each trial. Conventionally, ILP is performed via standard thoracotomy, and the resulting surgical stress can adversely affect both short- and long-term outcomes after this treatment [10,11].

Video-assisted thoracic surgery (VATS) has been established as a less invasive method of treating various thoracic diseases, in comparison to conventional surgery [12-14]. Excellent long-term outcomes after VATS resection of primary and metastatic lung tumors are reported [10-12], probably because of preserved immune function or depressed cytokine production [15,16]. Performance of ILP under VATS instead of conventional surgery lead to favorable outcomes after ILP treatment as well as facilitate patient participation in clinical trials of ILP. The aim of this experimental study was to establish a technique for performing ILP under VATS to treat unresectable lung malignancies.

2. Materials and methods

2.1. Animals

Ten canines weighing 8-13 kg were used in this study. Animals were treated in accordance with the Animal Welfare Act and the United States National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals (NIH publication 85-23, revised 1985), and the study protocol was approved by our Institutional Animal Care Committee. The animals were bred in a standard manner and were allowed...
free access to food and water in a temperature-controlled environment with a 12-h light and dark cycle. The animals were assigned to undergo either VATS-ILP (n = 5) or conventional ILP (n = 5) with cisplatin solution (50 μg/ml).

2.2. VATS-ILP

Before the start of VATS-ILP, the animals were given 10 mg/kg ketamine intramuscularly, then 10 mg/kg thiopental and 1 mg/kg suxamethonium intravenously. The animals were intubated and ventilated with equal amounts of nitrous oxide and oxygen in combination with halothane (1-1.5%), by means of a mechanical ventilator. Cisplatin (Sigma, St Louis, MO) was used as the antitumor agent because of its well-known activity and efficacy against a wide variety of tumors. After the right groin was shaved and disinfected, a 9F sheath was placed in the femoral vein. A 7.5F balloon occlusion catheter (Swan-Ganz oximetry thermodilution catheter, 750HF75; Baxter International, Irvine, CA) was introduced into the left pulmonary artery under fluoroscopic guidance. When the catheter was positioned appropriately and the animal had been given 2 mg/kg heparin intravenously, the balloon was inflated and contrast material was injected to ensure that the inflated balloon was occlusive. Animals were then placed in a decubitus position. A 10 mm thoracic port was placed in the sixth intercostal space to introduce the thoracoscopy (Surgiview, Auto Suture, USA). A 4- to 5-cm mini-thoracotomy was created through the fourth intercostal space, and each left pulmonary vein was exposed and encircled with tape. An 8F drainage cannula (Atom Multipurpose Tube, Atom Medical Co., Japan) with an angled, rigid stylet was introduced into each pulmonary vein through the left auricular appendage under thorascopic guidance (Fig. 1). The drainage cannulas were connected to a closed suction device, and the effluent was continuously suctioned out (50 cmH2O) and never reperfused. ILP was performed for 20 min at a flow rate of 30 ml/min with cisplatin solution (50 μg/ml). After perfusion, the lungs were flushed with buffered hetastarch solution (Salines, Kyorin Pharmaceutical Co., Japan) for 5 min at a flow rate of 30 ml/min. All cannulas were then removed, and the chest was closed.

2.3. Conventional ILP

For conventional ILP, left thoracotomy was performed through the fifth intercostal space, and left pulmonary artery and the left pulmonary veins were exposed and encircled with tape. After intravenous administration of heparin (2 mg/kg), vascular clamps were placed on the proximal left pulmonary artery. An 8F cannula was inserted into the left pulmonary artery through a purse-string suture. After purse-string suturing of the left auricular appendage, 8F drainage cannulas were introduced in each pulmonary vein. ILP was performed for 20 min at a flow rate of 30 ml/min with cisplatin solution (50 μg/ml).

2.4. Systemic and lung toxicity

Systemic toxicity was evaluated by daily measurement of the animal’s body weight after perfusion. Renal function and white blood cell (WBC) counts were assessed at the start of perfusion and 1, 3, 7, 14, 21, and 28 days after perfusion. Lung toxicity was evaluated by measurement of serum angiotensin-converting enzyme (ACE) levels and serum lactate dehydrogenase (LDH) levels at the start of perfusion and 1, 3, 7, 14, and 21 days after perfusion. These two factors were tracked because serum ACE is known to reflect endothelial cell damage and serum LDH is known to be associated with pneumocyte injury. Histologic changes in perfused lung tissue harvested at the completion of ILP and at autopsy were also evaluated. All animals were killed and autopsied on day 21 after the procedure.

2.5. Pharmacokinetics

Pharmacokinetics of ILP were evaluated by measurement of total platinum concentration with flameless atomic absorption spectroscopy. To measure the plasma concentration of total platinum, blood samples were collected at 10 and 20 min after the start of perfusion and 0.5, 1, 4, and 24 h after its completion. The caudal part of the perfused left lung was harvested immediately after ILP to measure the tissue concentration of total platinum.

2.6. Statistical analysis

Values are expressed as mean ± SD. Differences in continuous data between the groups were analyzed by unpaired t-test. Significance was accepted at P < 0.05.

3. Results

3.1. Systemic toxicity and lung toxicity

All animals survived the perfusion procedure without adverse reactions (i.e. uncontrolled bleeding, air embolism,
or respiratory failure), and there were no technical difficulties. VATS-ILP was performed through a significantly smaller thoracotomy than was used at conventional ILP (4.7 ± 0.4 cm for VATS-ILP vs. 12 ± 0.7 cm for conventional ILP, P < 0.001). No abnormality in the serum blood urea nitrogen or creatinine level was found in any animal. Changes in body weight, WBC count, serum ACE level, and serum LDH level after ILP are summarized in Table 1. Better recovery of body weight was observed during postoperative days 14-21 in the VATS-ILP group than in the conventional ILP group, although the differences were not statistically significant. Both the serum ACE level and serum LDH level were temporarily impaired within 3 days after ILP but recovered toward the baseline values thereafter. No significant difference was observed between the groups in WBC count, serum LDH level, or serum ACE level at any time point (all, P > 0.05). Both VATS-ILP and conventional ILP resulted in mild perivascular and peribronchial edema accompanied by minimal hemorrhage and thickening of the alveolar walls just after ILP, but these changes were almost completely resolved by postoperative day 21. Wet-to-dry weight ratios of treated lung tissues obtained just after perfusion are shown in Table 1. No significant difference was observed between the groups.

### Table 1

| Days after ILP | VATS-ILP (n=5) | Conventional ILP (n=5) | P  
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Body weight (% of baseline value)</td>
<td></td>
<td></td>
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<tr>
<td>1 day</td>
<td>95.7 ± 1.6</td>
<td>98.1 ± 2.9</td>
<td>0.15</td>
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<tr>
<td>7 days</td>
<td>90.5 ± 2.7</td>
<td>92.3 ± 5.1</td>
<td>0.51</td>
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<tr>
<td>14 days</td>
<td>92.3 ± 2.7</td>
<td>91.5 ± 6.7</td>
<td>0.81</td>
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<tr>
<td>21 days</td>
<td>95.5 ± 2.4</td>
<td>93.7 ± 5.9</td>
<td>0.55</td>
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<tr>
<td>White blood cell count (cells/mm³)</td>
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<tr>
<td>1 day</td>
<td>22720 ± 3000</td>
<td>26300 ± 4892</td>
<td>0.20</td>
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<tr>
<td>3 days</td>
<td>15400 ± 4009</td>
<td>14840 ± 6199</td>
<td>0.87</td>
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<tr>
<td>7 days</td>
<td>11540 ± 1704</td>
<td>12260 ± 8324</td>
<td>0.85</td>
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<tr>
<td>Serum ACE (IU/ml)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1 day</td>
<td>3.1 ± 1.1</td>
<td>3.2 ± 1.0</td>
<td>0.98</td>
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<tr>
<td>3 days</td>
<td>3.3 ± 0.9</td>
<td>3.3 ± 0.9</td>
<td>0.97</td>
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<tr>
<td>7 days</td>
<td>5.1 ± 2.4</td>
<td>4.4 ± 1.1</td>
<td>0.55</td>
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<tr>
<td>Serum LDH (IU/ml)</td>
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</tr>
<tr>
<td>1 day</td>
<td>163 ± 129</td>
<td>205 ± 122</td>
<td>0.61</td>
</tr>
<tr>
<td>3 days</td>
<td>86.4 ± 36.5</td>
<td>154 ± 135</td>
<td>0.31</td>
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<tr>
<td>7 days</td>
<td>63.4 ± 15.4</td>
<td>139 ± 79.4</td>
<td>0.07</td>
</tr>
<tr>
<td>Wet-to-dry weight ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 day</td>
<td>4.0 ± 0.6</td>
<td>4.3 ± 0.6</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. VATS, video-assisted thoracic surgery; ILP, isolated lung perfusion; ACE, angiotensin-converting enzyme; LDH, lactate dehydrogenase; 0 day, just after the ILP.

### 3.2. Pharmacokinetics

Plasma and tissue concentrations of total platinum are shown in Fig. 2. Both VATS-ILP and conventional ILP delivered a high dose of cisplatin to the treated lung without significant systemic leakage. Note that both VATS-ILP and conventional ILP delivered a high dose of cisplatin to the treated lung without significant systemic leakage. Barr et al. have previously reported that the platinum concentration in perfused lung tissue is dependent on both the perfusate cisplatin concentration and perfusion time [18,19]. In contrast, the platinum concentration in tumor tissue is independent on both the perfusate cisplatin concentration and perfusion time but is inversely dependent on tumor weight if the cisplatin concentration in perfusate is more than 25 μg/ml [19]. Therefore, we proposed that only small tumors should be treated by ILP; large tumors should be resected concurrently with this treatment. Now that ILP can be performed through an approach similar to that for VATS metastasectomy, VATS-ILP may serve as an adjuvant therapy if it is followed by complete metastasectomy.

We showed previously that ILP was superior to systemic chemotherapy in terms of the antitumor effect of cisplatin in lung tumor-bearing rats [20]. However, as is reported in clinical cases of isolated limb perfusion for unresectable sarcoma [21,22], simple exposure to cisplatin via ILP may
have limited antitumor efficacy. Addition of hyperthermia [23], hypertensive chemotherapy [24], and an additional drug [25] should be considered to improve the therapeutic efficacy of ILP. Attempts should also be made to lessen the surgical stress induced by ILP, which could have an adverse effect on the treatment outcome. VATS is recognized as a minimally invasive surgical treatment for lung cancer [12–17], and most necessary surgical treatment can be accomplished by VATS. Clinical trials of VATS-ILP in combination with other modalities, such as hyperthermia, are warranted to determine whether combined treatment will enhance the therapeutic effect of cisplatin administered via VATS-ILP.

In conclusion, we established a canine model in which the pharmacokinetic potential of VATS-ILP was shown to be similar to that of conventional ILP. Further study of this treatment procedure and its potential clinical application should prove fruitful.

References