Intrapleural Hyperthermic Perfusion for Malignant Pleural Effusion Under Video-Assisted Thoracoscopic Surgery

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Research

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Abstract

Background: Patients with malignant pleural effusion (MPE) have a poor prognosis. Most patients are treated with tube thoracostomy and sclerotherapy but with a not satisfactory control rate of pleural effusion. This study aims to report the effect of intrapleural hyperthermic perfusion for MPE which is a standard practice at our center.

Methods: This is a retrospective study of consecutive patients with MPE treated with hyperthermic perfusion from one single Institute. The procedure was done by perfusing the pleural cavity under video-assisted thoracoscope with 43.0°C distilled water using a standard extracorporeal circuit for 60 minutes. The efficacy of treatment was classified as follows: 1. complete response (CR; no re-accumulation of pleural effusion after IPH for at least four weeks); 2. partial response (PR; pleural effusion was reduced by 50% and this situation was sustained for four weeks; 3. no consequence (NC; pleural effusion was not reduced.

Results: From January 2014 through December 2018, a total of 31 patients with MPE were treated using this technique. There were no serious reportable clinical complications associated with the procedures. The response rate was 100%, with 67.7% of PR and 32.3% of CR. The survival time ranged from 2 to 46 months, with a median survival of 12 months. The survival time of the patients received TKI treatment after IHP ranged from 13 to 45 months, with a median survival of 28 months. Multivariable analysis showed that TKI treatment (P=0.013) and male gender (P=0.004) were independent prognosis factors.

Conclusions: Intrapleural hyperthermic perfusion is a feasible and safe strategy for patients with malignant pleural effusion.

Introduction

Malignant pleural effusion commonly occurred in advanced malignancies[1]. It is estimated that more than 15,000 MPE case occur in the United States every year[2]. Repeated thoracentesis and chest tube drainage is the usually used for treatment of MPE but without satisfactory results[3, 4]. The patients with MPE had a poor prognosis which reported to be with a 30-day mortality of 29-50% and median survival of 3-12 months[5-7]. Currently, there is no standard treatment for MPE patients which could provide a good control of pleural effusion and long survival. Intrapleural perfusion with hyperthermic chemotherapy (IPHC) is an effective approach by eradicating cancer cells with hyperthermic liquid combined with chemotherapeutic agents such as cisplatin[8]. The hyperthermia combined with chemotherapeutic agents synergistically decrease malignant cell survival. It was reported MPE patients treated with IPHC significantly prolonged survival to a median time of 19 months[9]. Distilled water was proved to be effective to eradicate free cancer cells and were commonly used for pleural or peritoneal lavage during surgery[10, 11]. Ba et al. reported B-ultrasound-guided continuous circulatory intrapleural hyperthermic perfusion with distilled water at 48 °C was a feasible and safe way to treat MPE and achieved a median survival of 13 months and 100% control rate of MPE[12].
Although several studies had demonstrated the effectiveness of IPHC, it was still not widely used in clinical practice. Our study aims to investigate the feasibility of VATS combined with intrapleural hyperthermic perfusion with distilled water to treat MPE patients.

**Patients And Methods**

Patients and study design

This was a retrospective study to analyze the clinical efficacy and survival benefit of intrapleural hyperthermic perfusion using distilled water to treat malignant pleural effusion. The records of patients with malignant pleural effusion who admitted to department of cardiothoracic surgery of Taizhou Hospital between January 2014 and December 2018 were reviewed. All patients received intrapleural hyperthermic perfusion using distilled water. Eligible criteria included patients aged ≥ 18 years and MPE confirmed by chest X-ray and/or computed tomography (CT) investigation, pleural cytology and/or biopsy. Patients’ cardiorespiratory function was able to tolerate general anesthesia. All patients underwent thorough examination before surgery including medical history, physical examination, computed tomography scan of the chest and abdomen, magnetic resonance scan of the brain, general bone scintigraphy to evaluate the primary tumor and metastases sites. The clinical stage of these patients was evaluated according to the eighth edition of the American Joint Committee on Cancer TNM staging. All patients signed an informed consent form.

The response of treatment was defined as follows: 1. complete response (CR; no re-accumulation of pleural effusion after IPH for at least four weeks); 2. partial response (PR; pleural effusion was reduced by 50% and this situation was sustained for four weeks; 3. no consequence (NC; pleural effusion was not reduced.

Surgical technique

VATS was performed for every patient under general anesthesia with double lumen endotracheal tubes ventilation. The vital signs were monitored through electrocardiogram. Invasive pressure and end tidal CO2 (etCO2) were also monitored. The patient was placed at 90° of lateral position. A 4 cm and 1 cm incision were made at the fourth and seventh intercostal space along the anterior and middle axillary line, separately, the latter of which was used for drainage after surgery. A trocar was inserted into the pleural cavity. Then, thoracoscope was put through the port and used to explore the pleural cavity for the extent of adhesion and tumor involvement. The adhesions, fibrinoid membrane restraining lung re-expansion and pleural effusion was removed with thoracoscopic equipment. Enough disseminated tumor tissues were achieved for biopsy. Then, 32F and 28F chest tubes were inserted into the above two ports as inflow and outflow catheters. The tubes were fixed to the chest wall with sutures and connected to a standard extracorporeal circuit (roller pump, heat exchanger and reservoir). A temperature sensor was put into the thoracic cavity for real-time monitoring.

Perfusion technique
After the procedure inside the thorax, the tubes were connected to the perfusion system and the extracorporeal circulation was started. The heating circuit system had preheated the distilled water to 43°C in advance. Then the pleural cavity began to perfuse and the ipsilateral lung collapsed. The flow rate was set between 1000 and 1500 ml/min. The temperature of the pleural cavity was maintained around 43°C. The perfusion procedure continued for 60 minutes. After perfusion, the thoracoscope was used to confirm no active bleeding, pulmonary air leakage. A 26F chest tube was placed through the seventh intercostal port in the thoracic cavity for drainage.

Follow-up

Patients were followed every two weeks for the first month and every month thereafter. Chest radiographs or ultrasound were done during the follow up. All patients were followed until they died. Survival was calculated from the date of surgery. The information of pleural effusion and overall survival were retrieved.

Statistical analysis

Data were presented as the mean ± standard deviation or the median and range. Overall survival was analyzed using Kaplan-Meier method with log-rank tests. The volume of pleural effusion was estimated through a three Dimension reconstruction of computed tomography of the chest with the software of Mimics Medical version 19.0 (Materialise, Belgium). IBM SPSS version 22.0 (IBM SPSS, Inc, Chicago, IL) was used for calculation. The Kaplan-Meier method with the log-rank test was used for survival analysis. The COX proportional hazards regression model was applied to perform univariate and multivariate analyses, and those variables that achieved a value of P <0.2 in univariate analysis were entered into the multivariable analysis. All statistical tests were 2-sided and a value of P <0.05 was considered to be statistically significant.

Results

Patient characteristics

Patients’ characteristics were summarized in Table 1. Of the 31 patients, 17 were males and 14 were females with a mean age of 62.3 years (median: 63 years; range: 39-81). The mean volume of pleural effusion estimated by CT was 1459±968ml. The KPS scores of these patients before IHP ranged from 30 to 90, with a median value of 55. 30 patients were diagnosed with lung cancer and 1 with renal clear cell carcinoma. Of the 30 patients, 28 patients were diagnosed with lung adenocarcinoma and 2 with squamous cell cancer. 2 patients had ever underwent lung cancer surgery. 13 patients only had pleural dissemination. 13 patients had ipsilateral, contralateral or bilateral lung metastases. 5 patients had multiple extrathoracic metastases including brain, bone or liver. 25 patients underwent gene test of EGFR with the specimen of pleural biopsy and 18 patients were diagnosed with EGFR sensitive mutation. 6 patients received Tyrosine Kinase Inhibitor treatment with Icotinib, Gefitinib or Osimertinib. No patients received systemic chemotherapy after surgery.
Table 1. Patients’ characteristics (n=31).
| Characteristics                                      | No. (%) |
|------------------------------------------------------|---------|
| Age, years (mean ± SD)                               | 62.3±10.1 |
| Gender                                               |         |
| Male                                                 | 17(54.8) |
| Female                                               | 14(45.2) |
| KPS, (range)                                         | 55(30-90) |
| Smoking history                                      | 8(25.8) |
| MPE volume, mL (mean ± SD)                           | 1459±968 |
| Primary cancer                                       |         |
| Lung adenocarcinoma                                  | 28(90.3) |
| Lung squamous cell cancer                            | 2(6.5)  |
| Renal clear cell carcinoma                           | 1(3.2)  |
| T stage                                              |         |
| cTX                                                  | 6(19.4)  |
| cT1                                                  | 3(9.7)   |
| cT2                                                  | 4(12.9)  |
| cT3                                                  | 2(6.5)   |
| cT4                                                  | 16(51.6) |
| N stage                                              |         |
| cN0                                                  | 13(41.9) |
| cN1                                                  | 3(7.3)   |
| cN2                                                  | 13(41.9) |
| cN3                                                  | 2(6.5)   |
| M stage                                              |         |
| cM1a                                                 | 17(54.8) |
| cM1b                                                 | 1(3.2)   |
| cM1c                                                 | 13(41.9) |
| EGFR mutation                                        |         |
| 19DEL                                                | 7(22.6)  |
|                        |        |
|------------------------|--------|
| L858R                  | 9(29.0)|
| 19INS                  | 1(3.2) |
| L861Q                  | 1(3.2) |
| EGFR wild type         | 7(22.6)|
| No genetic testing     | 6(19.4)|
| TKI treatment          | 6(19.4)|

Clinical efficacy and Survival

All patients re-evaluated pleural effusion after IHP. The response rate was 100%, with 67.7% of PR and 32.3% of CR. The median hospital stay postoperative was 7 days. Follow-up after IHP ranged from 2 to 46 months. The survival time ranged from 2 to 46 months, with a median survival of 12 months. The survival time of the patients received TKI treatment after IHP ranged from 13 to 45 months, with a median survival of 28 months. The OS curves of patients are shown in Fig 1. The 1-year and 2-year survival rates were 54.8% and 16%. Univariate analysis of predictors of OS showed that male gender (P=0.007), no TKI treatment (P=0.027) and clinical efficacy of PR (P=0.024) were associated with poorer prognosis. In multivariable analysis, TKI treatment (P=0.013) and male gender (P=0.004) remained independent prognosis factors (Table 2, 3).

Table 2. Univariate COX analysis of overall survival of the patients received IHP.
| Variable                        | HR  | 95%CI         | P value |
|--------------------------------|-----|---------------|---------|
| **Clinical efficacy**          |     |               |         |
| PR                             |     | Reference     |         |
| CR                             | 0.337 | 0.131-0.868  | **0.024** |
| KPS score                      |     |               |         |
| ≤50                            |     | Reference     |         |
| ≥50                            | 0.82  | 0.376-1.785  | 0.616   |
| **TKI treatment**              |     |               |         |
| No                             |     | Reference     |         |
| Yes                            | 0.501  | 0.271-0.923  | **0.027** |
| Serum CEA level, ng/ml         |     |               |         |
| <5                             |     | Reference     |         |
| ≥5                             | 0.58  | 0.238-1.411  | 0.23    |
| **Gender**                     |     |               |         |
| Female                         |     | Reference     |         |
| Male                           | 3.072  | 1.360-6.939  | **0.007** |
| Age, years                     |     |               |         |
| ≤60                            |     | Reference     |         |
| ≥60                            | 1.957  | 0.837-4.575  | 0.121   |
| Smoking history                |     |               |         |
| No                             |     | Reference     |         |
| Yes                            | 2.223  | 0.940-5.259  | 0.069   |
| Histologic type                |     |               |         |
| others                         |     | Reference     |         |
| Lung adenocarcinoma            | 1.229  | 0.288-5.241  | 0.781   |
| **EGFR mutation**              |     |               |         |
| Wild type                      |     | Reference     |         |
| Mutation                       | 0.673  | 0.309-1.465  | 0.318   |
| T stage          |           |           |
|------------------|-----------|-----------|
| TX, T1 or T2     | Reference |           |
| T3 or T4         | 0.987     | 0.445-2.186 | 0.974 |
| N stage          |           |           |
| N0 or N1         | Reference |           |
| N2 or N3         | 1.545     | 0.712-3.351 | 0.271 |
| M stage          |           |           |
| M1a              | Reference |           |
| M1b or M1c       | 1.271     | 0.582-2.773 | 0.548 |

Table 3. Multivariate COX analysis of overall survival of the patients received IHP.

| Variable              | HR    | 95%CI           | P value |
|-----------------------|-------|-----------------|---------|
| Clinical efficacy     |       |                 |         |
| PR                    |       |                 |         |
| CR                    | 0.755 | 0.241-2.361     | 0.629   |
| TKI treatment         |       |                 |         |
| No                    |       |                 |         |
| Yes                   | 0.139 | 0.029-0.662     | **0.013** |
| Gender                |       |                 |         |
| Female                |       |                 |         |
| Male                  | 5.664 | 1.715-18.705    | **0.004** |
| Smoking history       |       |                 |         |
| No                    |       |                 |         |
| Yes                   | 0.701 | 0.250-1.964     | 0.499   |
| Age, years            |       |                 |         |
| ≤60                   |       |                 |         |
| >60                   | 1.358 | 0.519-3.553     | 0.533   |

Adverse effects and complications
There were no serious complications after IPH treatment. No patients were admitted to ICU and there was no perioperative death. A few patients experienced mild gastrointestinal reactions which was attributed to adverse effects of anesthesia.

**Discussion**

Our study shows that intrapleural hyperthermic perfusion with 43°C distilled water under VATS provides a feasible and safe way for treating MPE.

There is still no effective way to treat disseminated pleural cancer with MPE. Patients with MPE had a poor prognosis and a low median survival, ranging from 6 to 18 months[13]. There were a lot of studies on hyperthermic intrathoracic chemotherapy (HITHOC) to locally control pleural effusion[9, 14-19]. Matsuzaki et al. reported a mean survival time of 20 months following lung resection and IHPC, but only 6 months without combination therapy[16]. However, the patients in combination therapy group were at early stage of MPE which may not truly reflected the efficacy of lung resection and IHPC.

Cisplatin was the most commonly used chemotherapeutic agent for IHP in studies[16, 17, 19]. however, there were some serious adverse effects with cisplatin such as renal toxicity, bone marrow suppression and cytotoxicity. The poor condition of MPE patients may not be able to tolerate the adverse effects of chemotherapeutic agents. Distilled water is commonly used for pleural lavage for pleural malignant tumors or for peritoneal lavage during surgery to eradicate free cancer cells[10, 11]. The cytocidal effects of hypotonic shock with distilled water on cancer cells was demonstrated in study[11]. Ba et al. reported that intrapleural hyperthermic perfusion using distilled water at 48 °C achieved a median survival of 13 months for MPE patients[12]. However, in Ba et al.’s study, the patients received IHP under B-ultrasound and patients with encapsulated pleural effusion or extensive pleural adhesions were excluded. VATS has an advantage of removing the pleural effusion and fibrinoid membrane restraining lung re-expansion which could improve the pulmonary function. The biopsy during surgery could provide enough fresh tissue specimens for gene test. The procedure of VATS surgery has already proved to be with less pain, rapid recovery and less hospitalized time.

The patients of EGFR mutation had a better survival compared with patients of wild type but with no statistical significance. Zhang et al. reported that EGFR domain mutation positive lung cancers were sensitive to intrapleural perfusion with hyperthermic chemotherapy complete treatment. Hyperthermia promoted accumulation of cisplatin in lung cancer cells and downregulated the EGFR protein level, leading to quenching of signal from EGFR and induction of apoptosis[20]. A further study is needed to confirm the better efficacy of intrapleural hyperthermic perfusion with distilled water on patients of EGFR mutation and the underlying mechanism.

TKI with or without pleurodesis was reported to be good on control of MPE in EGFR-mutant NSCLC patients. The progression free survival without re-accumulation of MPE achieved 21.7 months and the overall survival was 31.1 months[21]. In our study, the median OS of patients received TKI treatment was as long as 28 months which was comparable with that of Kashiwabara et al.
Limitations

There are some limitations in our study. First, this is a retrospective study with a small number of patients. Second, this is a single-arm study without a comparison of control group. Third, there was a decent of heterogeneity among patients in our group.

Conclusion

Intrapleural hyperthermic perfusion with 43°C distilled water under VATS is a feasible and safe treatment for patients with MPE. It can effectively remove the pleural effusion and prevented the effusion re-accumulation. Larger studies are still needed before it was widely used.

Declarations

Ethics approval and consent to participate: The study protocol was approved by the Ethics Committee of Taizhou Hospital and written informed consent was obtained from every study participant.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions

Minhua Ye and Jiang Jin had the idea for the article. Yulian Lin and Limin jia collected the data. Min Kong and Xinxin Wang performed the literature search and data analysis. Xinxin Wang drafted the article and Minhua Ye critically revised the work. All authors read and approved the final manuscript.

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