

Effect of hyperthermic intra-thoracic chemotherapy (HITHOC) combined with Crizotinib in the treatment of malignant pleural effusion

Lili Liu¹, Wei Li^{2,3}, Helong Zhang¹, Martin Ryu³

1. Department of Oncology, Tangdu Hospital, The Fourth Military Medical University, Xi'an, China
2. Department of Respiratory Diseases, Xijing Hospital, The Fourth Military Medical University, Xi'an, China
3. Xi'an Good Doctor Medical Science and Technology C. Ltd., Xi'an, China

Introduction

Oncogenic fusion genes of EML4 and anaplastic lymphoma kinase (ALK) represent 2~7% as a subgroup of NSCLCs [1]. Recent studies have shown that 58~72% NSCLC patient with positive gene fusion of *echinoderm microtubule associated protein-like 4 (EML4)* and *anaplastic lymphoma kinase (ALK)* responded to anti-ALK agents such as crizotinib or ceritinib [2, 3]. However, late stage NSCLC patients often have malignant pleural effusion (MPE) and do not response to traditional treatment of MPE, i.e. thoracentesis plus intra-pleural injection of cytotoxic drugs [4, 5]. Here, we report experience and result of hyperthermic intrathoracic chemotherapy (HITHOC) plus ALK inhibitor for treatment of patients with MPE and positive *ALK* gene fusion.

Patients

Three NSCLC-MPE patients were positive for *EML4-ALK* gene fusion as diagnosed by RT-PCR assay on the cellular specimens collected from the pleural effusion.

HITHOC treatment

The patient was at sit position and two puncture points were determined by the ultrasound. After topical disinfection and anesthesia, two 14G size of central venous catheters were placed into the pleural cavity and connected to the "Inlet" and "Outlet" ports of the GD-HIPEC device (Xi'an Good Doctor Medical Science and Technology Co. Ltd.). Bloody pleural effusion was first lavaged with 1000~2000 mL pre-warmed saline using the GD-HIPEC machine under "One-

way lavage” mode. After completion of the lavage, a sealed hyperthermic (41~43°C at the outlet port) circulation between the GD-HIPEC device and the patient’s pleural cavity was then initiated. Cisplatin (12.5 mg) was then injected into the hyperthermic circulation system and the HITHOC lasted for 60 minutes for each therapy.

Each therapeutic course (2 times HITHOC treatment) was given in 3 weeks (21 days) apart and the patient was given crizotinib (250mg each time, twice per day) during the intervals.

Results

After being treated with HITHOC and crizotinib, one patient had complete remission (CR), the rest two patients had partial remission (PR), and overall effective rate (RR=CR+PR) was 100%. Patients were followed-up for up to 28 months from August 2013 till the date of data collection in January, 2016.

After 2 course (4 times) of HITHOC therapy with cisplatin, MPE of the Patient #1 was significantly reduced (**Fig 1**), and symptoms were relieved. The patient was further treated with crizotinib and had 11 months of progression-free survival (PFS) till the date of data collection.

MPE of Patient #2 was significantly reduced after 2 therapeutic courses of HITHOC (**Fig 2**). The patient was further treated with cisplatin and pemetrexed for total 6 courses. Afterwards, the patient had brain metastasis, which was effectively treated with crizotinib. This patient’s OS was 18 months and PFS was 13 months.

After one therapeutic course of HITHOC treatment, the #3 patient’s malignant effusion was completely controlled and symptoms were completely relieved (**Fig 3**). The patient was further treated with crizotinib and PFS was 20 months till the date of data collection.

None of the three patients had severe toxic side effects.

Conclusion

The current study reports experience of a novel treatment strategy in three cases of recurrent or advanced-stage NSCLC-MPE, that is, HITHOC with cisplatin followed by personalized anti-ALK therapy with crizotinib. MPE was

effectively controlled after 1~2 therapeutic courses of HITHOC, and the patients' OS and PFS were significantly extended. Findings of the current study demonstrated that HITHOC followed by anti-ALK treatment is safe and effective in the treatment of advanced-stage NSCLC-MPE with positive *ALK* gene fusion.

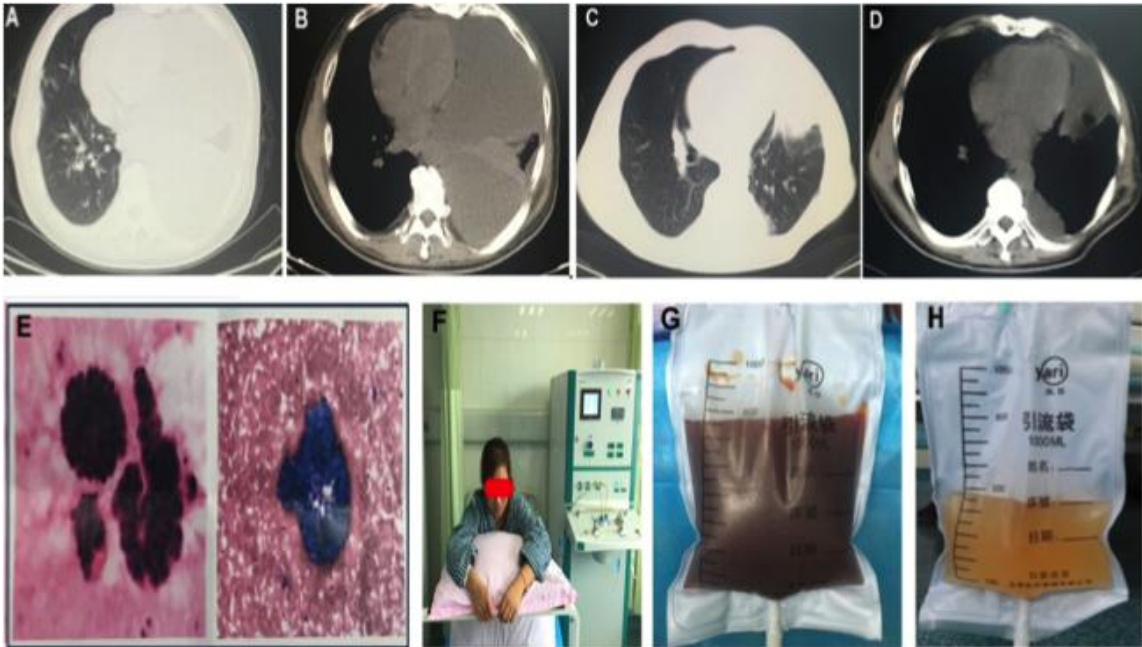


Figure 1. Recurrent malignant pleural effusion after surgical resection of lung adenocarcinoma. Panels A, B, C, D: CT images before HITHOC (A and B), after two therapeutic courses (C and D). **Panel E:** Cytologic examination of the lavage fluid demonstrated adenocarcinoma before HITHOC. **Panel F:** Patient sat up and received HITHOC therapy for one hour. **Panels G, H:** Color change of the pleural effusion lavage before HITHOC (G), after two therapeutic courses (H).

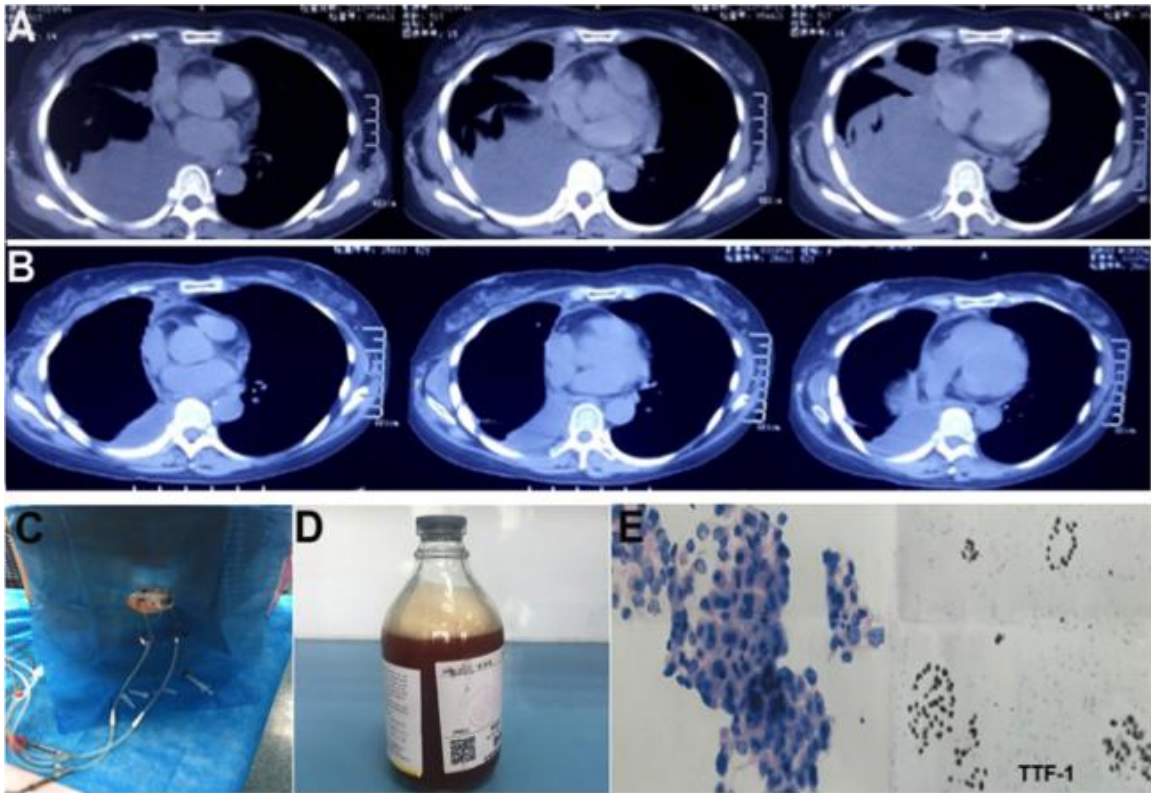


Figure 2. Recurrent malignant pleural effusion after surgical resection of lung adenocarcinoma. Panels A, B: CT images before HITHOC (A), after two therapeutic courses (B). **Panel C:** Patient sat up and received HITHOC therapy for one hour. **Panels D:** Color change of the pleural effusion lavage before HITHOC. **Panel E:** Cytologic examination of the lavage fluid demonstrated adenocarcinoma before HITHOC.

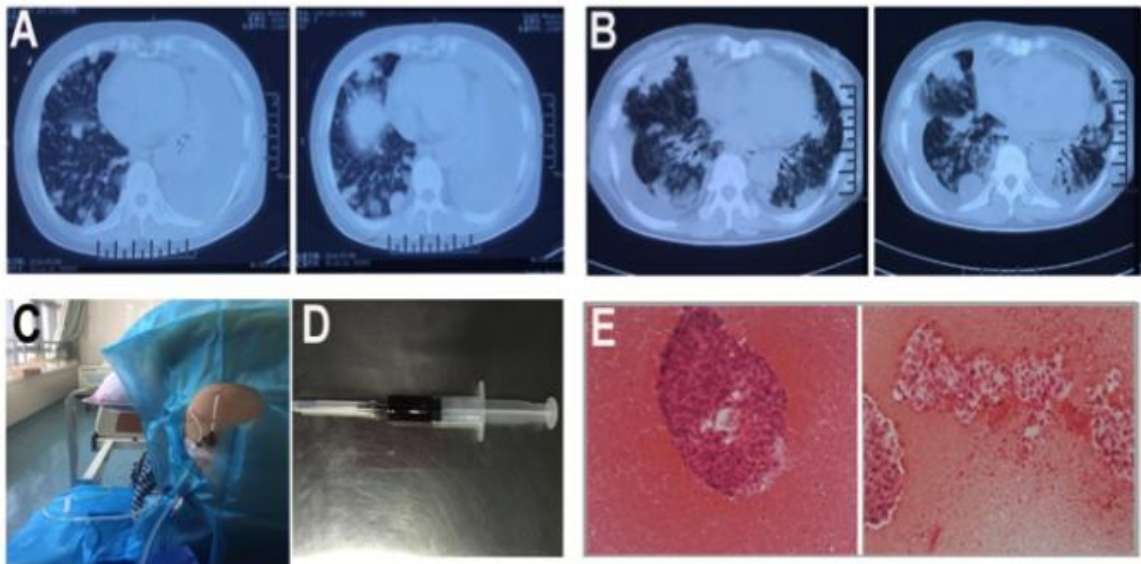


Figure 3. A late stage lung squamous cell carcinoma presented with malignant pleural effusion after systemic chemotherapy. Panels A, B: CT images before HITHOC (A), after one course of HIPEC therapy (B). **Panel C:** Patient sat up and received HITHOC therapy for one hour. **Panels D:** Color change of the pleural effusion lavage before HITHOC. **Panel E:** Cytologic examination of the lavage fluid demonstrated adenocarcinoma before HITHOC.

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