Video Article

Endobronchial Ultrasound-guided Intratumoral Injection of Cisplatin for the Treatment of Isolated Mediastinal Recurrence of Lung Cancer

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Abstract

Isolated hilar and mediastinal recurrence (IMHR) following external beam radiation therapy (EBRT) in patients with lung cancer is common. These patients do not have many treatment options and are usually offered palliative chemotherapy or best supportive care. Endobronchial ultrasound (EBUS)-guided intratumoral injection of cisplatin (ITC) is a novel approach for these patients. The procedure is performed under conscious sedation. The lesion is located with a bronchoscopy using EBUS, and a 22-gauge EBUS needle is advanced through the working channel of the scope and locked in position. Under ultrasound guidance, the wall of the tracheobronchial tree is punctured and the needle is moved into the target lesion. The needle stylet is then removed and cisplatin (40 mg/40 mL) is injected into the lesion. One to two sites are treated per session. Details of the procedure are described in the protocol section of paper. At our center, 50 sites were treated in 36 patients (19 males, 17 females). The mean age of our cohort was 61.9 ± 8.5 years. We performed final analyses on 35 patients and 41 sites. 24/35 (69%) had complete or partial response (responders), whereas 11/35 (31%) had stable or progressive disease (non-responders). Overall, survival in our group was 8 months (95% CI of 6-11 months), with patients who responded having significantly better survival than the ones who did not.

Video Link

The video component of this article can be found at <https://www.jove.com/video/54855/>

Introduction

Lung cancer is the most prevalent cancer worldwide in both men and women and accounts for 1 in 5 of all cancer-related deaths. It has a case fatality rate of 0.87^{1,2}. Recurrence after initial treatment accounts for most deaths in patients with lung cancer. Therapeutic options for recurrent lung cancer are limited. Recurrent lung cancer also leads to significant impairment in quality of life and to significant caregiver burnout and requires additional supportive care, all of which decrease the likelihood of acceptance and tolerance to further interventions³.

Nearly 30% of patients with NSCLC have locoregional recurrence after radiation⁴. Treatment options for these patients are limited and include systemic chemotherapy, which has an objective response rate of only 10%^{5,6}. Although repeat chest radiation is feasible, it has been studied mainly for palliative purposes and symptom relief and has not been used for disease remission³.

At our institution, all patients with isolated mediastinal and hilar recurrence (IMHR) accessible through bronchoscopy were treated with an endobronchial ultrasound (EBUS)-guided transbronchial intratumoral injection of cisplatin (ITC). Concurrent treatment with systemic chemotherapy and/or external beam radiation therapy (EBRT) was allowed as per the treating oncologists' discretions. This manuscript highlights the safety, efficacy, feasibility, and detailed methods of the protocol used at our institution.

Protocol

Data on all patients treated with EBUS-guided cisplatin were reviewed. The institutional review board at the University of Florida approved this study (#IRB201400823). All data was prospectively collected and retrospectively analyzed. Use the following enrollment criteria.

1. Patient Selection

1. Select patients between the ages of 18 and 80 years who have a biopsy-confirmed non-small cell lung cancer (NSCLC) or small cell lung carcinoma (SCLC) and have a pathologically-confirmed recurrence. Enroll patients who have received at least 50 Gy of radiation to the hilar and mediastinal structures for 6 months or longer. Include patients with limited recurrence to the hilar, mediastinal, and peribronchial structures (lymph nodes, nodules, and masses) accessible through EBUS and distant metastases.

2. Present all such patients to a multi-disciplinary thoracic oncology tumor board and obtain consensus on proceeding with the intratumoral cisplatin due to a lack of other localized therapeutic options. The decision to proceed with EBUS-guided ITC should be a joint recommendation of the institutional thoracic oncology tumor board.

2. Endobronchial Ultrasound (EBUS)-guided Cisplatin Injection

1. Use a convex-probe EBUS, which has a built-in ultrasound probe on a flexible bronchoscope and enables real-time visualization of hilar, mediastinal, and peribronchial structures for ITC.
2. Ensure that the patients abstain from oral food and fluids for at least 6 h prior to the procedure.
3. Create an aqueous cisplatin solution at a concentration of 1 mg/mL with a maximal dose of 40 mg per session, based on previously-published literature^{9,10}. Dissolve lyophilized cisplatin powder in 0.9% NaCl solution just before use.
4. Give 10 mg of dexamethasone and 8 mg of ondansetron intravenously at the beginning of the procedure to prevent nausea.
5. Perform the procedure with conscious sedation using midazolam and fentanyl intravenously (IV). Use topical anesthesia in the form of 5 mL of 4% lidocaine nebulization prior to the procedure.
6. Start out with an IV injection of 2 mg of midazolam and 50 µg of fentanyl. Reassess the patient every 1-2 min and give an additional 1 mg midazolam and 25 µg fentanyl bolus to achieve and maintain conscious sedation (a minimally depressed consciousness such that the patient is able to continuously and independently maintain a patent airway, retain protective reflexes, and remain responsive to verbal commands and physical stimulation). Do not exceed the maximal permissible doses of fentanyl and midazolam, 200 µg and 10 mg, respectively.
7. Use standard monitoring, including a continuous 3-lead electrocardiogram monitoring the heart rate, continuous pulse oximetry, and respiratory rate measurements. Provide local anesthesia and supplemental O₂ as required.
8. Advance the scope through the vocal cords in the airways. Identify and locate the target lesion.
9. Turn on the EBUS processor and inflate the balloon at the tip of the scope using 1-2 mL of normal saline. Flex the scope across the airway wall and locate the lesion. The location of the lesion will depend on CT/PET findings, but some of the common sites include the subcarinal area, the right and left paratracheal areas, and the right and left hilar areas.
10. Deploy a 22 G EBUS needle that is housed in a sheath through the working channel of the scope and lock it in position.
NOTE: Although there are no precise surgical coordinates for the injection site, some of the commonly-treated sites include the subcarinal (medially at the junction of the left and right main bronchi), the right paratracheal (laterally at the right main bronchus, just above the right upper lobe orifice), the left paratracheal (at the junction of the distal trachea and the left main between the arch of the aorta and the left pulmonary artery), the right hilar (laterally at the proximal bronchus intermedius, below the right upper lobe opening), and the left hilar (at the junction of the left upper lobe and the left lower lobe bronchi).
11. Under real-time ultrasound guidance, puncture the tracheobronchial wall and place the needle in the target lesion. Remove the stylet within the needle and inject cisplatin into the lesion 10 mL (1 mg/mL of cisplatin) at a time. Retract the needle within the sheath.
12. Treat each lesion with four punctures per session at different locations to facilitate the injection of the medication throughout. Inject 10 mg of cisplatin per puncture.
13. Treat one to two lesions per session. If more than one lesion is treated per session, inject each site with 20 mg of cisplatin, with total dose per session not exceeding 40 mg.
14. Remove the needle from the working channel of the scope.
15. Suction any additional drug from the distal airways and remove the bronchoscope.
16. Allow the patients to recover as per hospital protocol and discharge them on the same day.
17. Repeat the cisplatin injection (steps 2.7-2.13) once a week for a total of 4 weeks (on days 1, 8, 15, and 22).
NOTE: Once treated, a particular lesion should never be considered for retreatment with ITC on subsequent encounters.

3. Post-injection

1. Evaluate the response by a follow-up chest computed tomography (CT) or a positron emission tomography (PET/CT) scan 8-12 weeks after the last treatment session. Define the local recurrence as the recurrence at the site of treatment and the regional recurrence as the recurrence in the mediastinum, hilum, or supraclavicular fossa.

Representative Results

The response was measured by follow-up imaging 8-12 weeks after therapy. The response was classified as complete remission (CR), partial remission (PR), stable disease (SD), progressive disease (PD), or unable to assess response based on RECIST 1.1 criteria⁸. Patients with CR and PR were considered responders, and the others were classified as non-responders. Secondary outcomes included response based on tumor histology, size of recurrence, and concurrent systemic therapy. The side effects and feasibility of the protocol were also analyzed.

Kaplan-Meier curves were used to estimate the survival probabilities. The survival and PFS for responders versus non-responders was compared by the log-rank test. Associations between response rates and other factors were examined using Fisher's exact test.

Figure 1 shows a detailed distribution of patients, sites, and site-specific responses. The final analysis included 35 patients and 41 sites. 69% of the patients were classified as responders (24/35), and 31% were non-responders (11/35). **Table 1** shows the outcomes of the treatment based on various sub-group analyses. The median survival for the group was 8 months (95% CI of 6-11 months): 10 months for responders (95% CI of 8-13 months) and 6 months for non-responders (95% CI of 3-10 months); this difference was statistically significant, with a p-value of 0.029 (**Figure 2**). **Figure 3** shows the difference in PFS between responders and non-responders.

Figure 1: Number of Patients Analyzed and Their Outcomes. A detailed flow diagram of the number of patients and sites treated initially and the number of patients and sites presented here for final analysis. [Please click here to view a larger version of this figure.](#)

Figure 2: Kaplan-Meier Curves for Overall Survival in Months Amongst Responders and Non-responders. These curves show that patients who responded to therapy demonstrated statistically-significant overall survival as compared to non-responders. [Please click here to view a larger version of this figure.](#)

Figure 3: Kaplan-Meier Curves for Progression-free Survival in Months Amongst Responders and Non-responders. Patients who responded to treatment had statistically-significant improvements in progression-free survival. [Please click here to view a larger version of this figure.](#)

		Responders	Non Responders	p value
1	Histology			0.84
-	Adenoca	13 (72%)	5 (28%)	
-	Squamous	7 (58%)	5 (42%)	
-	Small cell	3 (75%)	1 (25%)	
-	Large cell	1 (100%)	0	
2	Concurrent systemic Rx			1
-	Chemo	5 (63%)	3 (37%)	
-	Radiation	2 (100%)	0	
-	None	17 (68%)	8 (32%)	
3	Size of lesion			0.066
-	≤1cm	8 (89%)	1 (11%)	
-	1.1-2 cm	10 (83%)	2 (17%)	
-	2.1-3 cm	3 (43%)	4 (57%)	
-	>3 cm	3 (43%)	4 (57%)	

Table 1: Response to ITC with cisplatin based on histology, concurrent systemic therapy and size

Table 1: Sub-group Analyses of Response to Cisplatin Based on a Few Select Variables. There was no statistically-significant difference in patient response based on tumor histology, size, or concurrent systemic therapy.

Discussion

Our manuscript focuses on the management of isolated mediastinal and hilar recurrences of lung cancer for patients in whom more radiation is not an option. The incidence of IMHR is approximately 9%¹¹. Different treatment options have been tried in these patients, including palliative chemotherapy, more external beam radiation therapy, or supportive care and surveillance. At our institution, we treat these patients with intratumoral cisplatin guided by bronchoscopy.

There has been a growing interest in intratumoral chemotherapy and immunotherapy over the last several years. One of the potential advantages of injecting chemotherapeutic agents into the tumor mass is that a significantly higher concentration (6-10 times) of the medication can be achieved in the tumor mass¹². Cisplatin is commonly used for the treatment of lung cancer as a part of combination systemic chemotherapy^{13,14}, and it has also been used intralesionally for head, neck, and malignant liver cancers^{15,16}. Additionally, it has been utilized endoscopically for palliation of obstructive esophageal cancers¹⁷ and injected into gastric tumors¹⁸. Based on available evidence and experience, we chose to use cisplatin as the chemotherapeutic agent of choice for bronchoscopic ITC.

The critical step in this protocol involves the proper patient selection. All patients should demonstrate in-field recurrence from a previous disease, should present isolated disease in the chest, and should be discussed at a multidisciplinary tumor board to confirm their limited therapeutic options. From a procedural perspective, the ability to identify the site of recurrent disease on EBUS and to advance the needle reliably into the diseased node is important. Cisplatin should be injected into the tumor in 10 mL aliquots. An attempt must be made to inject 40 mg in four separate passes at different areas on the node. After injecting the drug, excess cisplatin should be suctioned from the distal airways. Due to concerns for developing bronchopleural fistula, concurrent radiation therapy to the same site is not recommended. Up to 2 sites can be treated in the same session. If more than one site is treated, each site should be injected with 20 mg of cisplatin.

In patients with stage III or stage IV NSCLC previously treated with chemotherapy who are treated with second-line chemotherapy, the median survival time is 4-10 months^{19,20}. However, no studies to date have looked into the survival among patients with isolated hilar and mediastinal recurrence of lung cancer following full-dose radiation therapy. The overall median survival of 8 months in our cohort is comparable to the number quoted in existing literature and would suggest a survival benefit compared to best supportive care only. Additionally, the localized cisplatin injection is tolerated much better and has fewer side effects as compared to systemic chemotherapy.

There are several limitations to our study, including retrospective design. Although we have a very well-structured protocol, its performance outside of our institution has not been studied. Serum and tumor concentration of the drug were not analyzed, and some patients were receiving systemic therapy, which could have confounded the results. However, we believe that the response seen in our cohort can largely be attributed to localized cisplatin injection^{7,12}.

EBUS-guided intratumoral injection of cisplatin is feasible, well-tolerated, and potentially safe and effective in patients with isolated hilar and mediastinal recurrence of lung cancer for whom no localized therapeutic options are available. Multicenter randomized trials should be conducted to further validate our findings.

Disclosures

The authors have nothing to disclose.

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