Endobronchial Chemotherapy in Malignant Airway Lesions of the Lung
Report of 3 Years Experience

Hamidreza Jabbarjadi, MD,* Shahram Kharabian, MD,* Mohammad Reza Masjedi, MD
Tracheal Disease Research Center, National Research Institute of Tuberculosis and Lung Disease
Shahid Beheshti University of medical sciences
Tehran, Niravaran, Darabad
IRAN

Email: drhrjabbari@yahoo.com

Abstract: Bronchoscopic palliative treatment is a modality that could reduce the symptoms in patients with inoperable lung cancer. Our interest is to study the palliative effect of intrabronchial chemotherapy using cisplatin, in patients with inoperable lung cancers. Between the years of 2003 and 2006, patients with unresectable lung cancer and endobronchial lesion were selected for tumor debulking via intrabronchial injection of cisplatin. After flexible bronchoscopy, maximum 20mL cisplatin with the concentration of 50 mg/100mL was injected into the bulk of the tumor through the special needle. The procedure was performed weekly for 4 sessions. After the end of fourth session, this procedure was done monthly. Patients were followed according to the symptoms, size of the involved lumen, and changes in the shape and size of intrabronchial lesion after local chemotherapy. A hundred patients were studied (72 men, 28 women). All of them diagnosed with inoperable lung cancer. According to the histology, they were categorized as adenocarcinoma (n=48), squamous cell carcinoma (n=32), and nonsmall cell lung cancer, unspecified (n=20). At the end of the forth session of local chemotherapy, the involved lumen was considerably opened (more than 25%) in 80 patients. We suggest that endobronchial chemotherapy with cisplatin could be used for debulking of the tumor in the cases with inoperable lung cancer.

Key-Words: endobronchial chemotherapy, bronchoscopy, lung Cancer

1 Introduction
Lung cancer is the foremost cause of death among all cancers and sexes,1 so 5-year survival of lung cancer, despite all therapeutic modalities, is 15%.2 Surgical resection still is a treatment of choice in resectable lung cancer.3 Unfortunately, the majority of patients with recently diagnosed lung cancer are not operable. Multiple studies suggested that tumor debulking has a considerable role in increasing survival and life expectancy in patients with inoperable lung cancer.4–8 There are multiple modalities which have been suggested for this palliative role.9 Some studies have reported the efficacy of intratumoral drug injection,10 since Hayata et al11 first developed this modality by bacillus Calmette-Guerin solution. Recently, antineoplastic effect of cisplatin have been shown.12,13 Our interest in this study is to present our experience with the efficacy of intrabronchial chemotherapy in palliative care of patients with inoperable lung cancer.

2 MATERIALS AND METHODS
Between the years of 2003 and 2006, patients with unresectable lung cancer and endobronchial lesion were selected for tumor debulking via intrabronchial injection of cisplatin at our institution. All aspects of this clinical study (ie, patient enrollment, informed consent) were conducted with approval of the Shahid Beheshti University of Medical Science, Investigational Review Board, and requiring ethical committee approval of such clinical medical studies. Informed consent was obtained from all patients enrolled in this study. The following variables were analyzed: age, sex, initial symptoms, computed tomography-scan, bronchoscopic report, histopathology, Karnofsky scale score, and the presence of distant metastasis. This study was carried out among patients with lung cancer in whom their tumors had led to obstruction of the bronchi. All patients were diagnosed with inoperable lung cancer. Patients who could not tolerate the flexible bronchoscopy, or had previous history of allergic reaction to cisplatin were excluded. The procedures were performed under local anesthesia through a flexible bronchoscope, Olympus BF-200, Japan. With
the patient in the supine position, the flexible bronchoscope was inserted transnasally into the tracheobronchial tree. Cisplatin was administered to all endoscopically visible tumoral tissue through a flexible 21 to 23-gauge needle. The needles, used for intratumoral injections, were manufactured for this purpose (Medwork Injection needle). To prevent damage to the working channel of the flexible bronchoscope, all needles were of retractable design. Cisplatin with the concentration of 50 mg/100mL was used for all the cases as the chemotherapeutic solution. Maximum 20mL cisplatin/cm2 of tumor mass was injected intratumorally (4 mg/cm2). The procedure was performed weekly for 4 sessions. After the end of forth session, these procedures were done monthly, for the rest of the life. In each session, patients’ symptoms, diameter of the lumen, and complications were recorded. These characters were compared with previous records. After 4 sessions, this procedure was performed monthly. In the cases of local recurrence of the tumor, maximum of 20mL cisplatin had been injected at the bulk of the tumor. Patients were followed according to the symptoms and the size of the lumen.

3 RESULTS
A hundred patients were studied (72 men, 28 women). The average age was 58 years in men and 61.5 years in women.
Symptoms
Before procedure initiation, patients’ symptoms were recorded. Initial symptoms included dyspnea (n=94), cough (n=90), sputum (n=80), nonmassive hemoptysis (n=68), fever and chills (n=56), massive hemoptysis (n=4), and chest pain (n=66).
Imaging
Radiographic changes according to the computed tomography-scan reports included atelectasis (n=46), lobar infiltration (n=34), diffuse infiltration (n=54), Para hilar consolidation (n=62), and pleural effusion (n=42).
Bronchoscopic Appearance
All lesions resulted in complete or partial obstruction. Size of the lumen was visually measured and it was recorded by videoscope device. Some patients had more than one obstructing lesion. Sites of the lesions included trachea (n=8), carina (n=42), left main bronchous (n=34), right main bronchous (n=48), left upper lobe (n=52), left lower lobe (n=32), right upper lobe (n=24), right lower lobe (n=76), and right middle lobe (n=40).
Figure 1 shows the sample appearance of airways before the procedure.
Histopathology
Histopathologic type of the lesions was obtained from patients’ record. They included squamous cell carcinoma (n=32), adenocarcinoma (n=48), and nonsmall cell lung cancer, unspecified (n=20).

Evaluation of Tumor Debulking
Intrabronchial injection of cytotoxic drugs was in most cases followed by an immediate endoscopically visible effect (Fig. 2). Endoscopic examinations 4 weeks after the beginning of the intrabronchial chemotherapy indicated that 52 of 100 patients had an increase in the airway lumen diameter of more than 50% (good response), and 28 patients showed an improvement of 25% to 50% (moderate response). In others, increase in the diameter of the lumen of airway after intrabronchial chemotherapy was less than 25% (poor response). Overall, debulking by intrabronchial chemotherapy was considered clinically satisfactory (>25%) in 80 of the 100 patients. The symptoms after the forth session were of dyspnea (n=60), cough (54), sputum (n=56), nonmassive hemoptysis (n=14), massive hemoptysis (n=0), fever and chills (n=40), and chest pain (n=66).
At the end of the forth session, radiologic findings were corrected only in 16%, but after 3 months, in 34% of the patients, infiltrations were corrected.

Follow up
Patients were followed for average of 21 months. It was ranged from 6 months up to 38 months. Average of symptom relief period was ranged from a month in the worst condition (with evidence of distant metastasis, Karnofsky performance scale lower than 30, and poor response to the procedure) and 13 months in the best
condition (without any evidence of distant metastasis, Karnofsky performance scale above 80 and good response to the procedure).

Complications

Complications included bleeding (9), hypoxia (12), tachycardia (35), hypertensive crisis (3), and pain (27). Hypertensive crisis was seen in patients with the previous of Patients Symptoms history of controlled hypertension. Bleeding and pain were controlled through diluted epinephrine (1/100,000) and 2% Lidocaine washing, respectively. Hypoxemia was treated via supplemental oxygen and hypertensive crisis controlled via intravenous infusion of nitroglycerine.

4 Discussion

The standard of care in locally advanced, surgically unresectable lung cancers, still includes systemic chemotherapy because of its survival benefit demonstrated in randomized trial.14–16 However, it is well known that the safety of systemic chemotherapy is severely limited by systemic toxicity.12 The effects of interventional bronchoscopic techniques (laser photo resection, cryotherapy, stent, etc.) in debulking of airway tumors have been shown in several studies.4–8 These modalities could reduce severe complications, such as postobstructive infection and hemoptysis, and increase the vital capacity. Multiple studies have been performed in the field of intrabronchial chemotherapy since 50 years ago. Hayata et al11 first developed intratumoral injection by bronchoscopy in the early 1970s.17,18 In that study, direct injection of bacillus Calmette-Guerin and some anticancer drugs into endobronchial tumors or infiltrated mucous membrane was used to manage endobronchial tumors.11 The latest studies of the cases with endobronchial injection of agents have been depicted in Table 2. Ethanol was a substance, widely used for debulking of obstructing lesions.19,20 There were many studies, performed by Dr Celikoglu et al21–23 during last decades about intratumoral chemotherapy. In recent years, cisplatin has been shown to be one of the most active single agents against lung cancer, frequently used in systemic chemotherapy.12,13 Multiple studies have demonstrated the efficacy of intratumoral chemotherapy via cisplatin in the field of liver, esophageal, and head and neck cancers.24 Tumoral lesions have 2 segments of intrabronchial segment (small part of tumor, known as iceberg) and extrabronchial segment (major segment, which has pressure effect on mediastinal organs). It has been proven that both segments necrotize and shrink during cisplatin injection.23 In our study, all patients had the history of systemic chemotherapy or external beam radiotherapy, because of their advanced disease. In Celikoglu et al study,21 patients received external beam radiation after the end of local chemotherapy period. The effects of radio sensitization of cisplatin have been proven by Scagliotti et al.25 In our study, as in Celikoglu et al23 experience, patients’ symptoms were considerably relieved after 4 sessions of local chemotherapy. At that time diameter of involved lumen was increased more than 25% in 80 cases. Average of symptom relief period in our study was about 240 days. It was ranged from a month in the worst condition, up to 13 months in the best condition. It depended on multiple factors including progression of tumor, the patient’s Karnofsky performance scale, and previous history of systemic chemo-radiotherapy. InWaechter et al26 study, 1-year and 2-year survival of the patients were 40% and 23%, respectively. Average survival time in Celikoglu study was 360 days.23 Similarly, failure of debulking of airway obstruction by laser photo resection or cryotherapy has been associated with poor progression in several studies.27 In our study, 18 cases experienced a symptom-relief period of more than 400 days. There were insignificant complications in our study similar to previous studies, which were controlled via simple efforts.

5 Conclusion

We suggest that intratumoral injection of cisplatin could reduce the severe symptoms of airway obstruction, hemoptysis (massive or nonmassive), and postobstruction pneumonias in patients with inoperable lung cancer. Further large-scale trials on endobronchial chemotherapy with or without external beam radiation therapy are warranted.

References:


Recent Researches in Modern Medicine

TABLE 2. Previous Clinical Trials in Endobronchial Chemotherapy

<table>
<thead>
<tr>
<th>Author</th>
<th>Agent</th>
<th>No. Patient</th>
<th>Rate of Symptom Relief (%)</th>
<th>Rate of Complications</th>
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<td>Sawa et al.</td>
<td>Ethanol</td>
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<tr>
<td>Liu et al</td>
<td>Cisplatin</td>
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