Lung Cancer xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Treatment of isolated mediastinal and hilar recurrence of lung cancer with bronchoscopic endobronchial ultrasound guided intratumoral injection of chemotherapy with cisplatin

Hiren J. Mehta[a,*], Abbie Begnaud[b], Andrea M. Penley[a], John Wynne[a], Paras Malhotra[c], Sebastian Fernandez-Bussy[d], Jessica M. Cope[e], Jonathan J. Shuster[f], Michael A. Jantz[a]

[a] Division of Pulmonary, Critical care, Sleep Medicine, University of Florida, College of Medicine, United States
[b] Division of Pulmonary, Critical care, Sleep Medicine, University of Minnesota College of Medicine, United States
[c] Division of Pulmonary, Critical care, West Virginia University Charleston Division, United States
[d] Interventional Pulmonology, Clinica Alemana-Universidad del Desarrollo, Santiago, Chile
[e] UF Health Shands Hospital, Department of Pharmacy, Gainesville, FL, United States
[f] Department of Health Outcomes and Policy, College of Medicine, University of Florida, United States

ARTICLE INFO

Article history:
Received 23 March 2015
Received in revised form
22 September 2015
Accepted 4 October 2015

Keywords:
Lung cancer recurrence
Sisplatin
endobronchial ultrasound

ABSTRACT

Purpose: A common pattern of recurrence in lung cancer after receiving full dose external beam radiation therapy (EBRT) to targeted sites is isolated mediastinal and hilar recurrence (IMHR). Treatment options for these patients are limited to palliative radiation, chemotherapy, and/or best supportive care. We describe our experience with treating IMHR with bronchoscopic endobronchial ultrasound (EBUS) guided intratumoral injection of cisplatin (ITC).
Methods: Patients treated between Jan 2009–September 2014 with ITC for IMHR were included. Patient demographics, tumor histology, size, concurrent therapy, location, number of sites treated, treatment sessions, and encounters were abstracted. Responses were analyzed on follow-up scans 8–12 weeks after the last treatment session using RECIST 1.1 criteria. Locoregional recurrence, progression-free survival (PFS), and overall survival were measured.
Results: 50 sites were treated in 36 patients (19 males, 17 females) with mean age 61.9 ± 8.5 years. Eight sites treated on subsequent encounters were excluded and one patient had an unevaluable response, leaving 35 patients and 41 sites for final analysis. 24/35 (69%) had complete or partial response (responders), whereas 11/35 (31%) had stable or progressive disease (non-responders). There were no significant differences in response based on histology, size, and concurrent therapy. Median survival for the group was 8 months (95% CI of 6–11 mo). Responders had significantly higher survival and PFS than non-responders. Two patients treated with concurrent EBRT, developed broncho-mediastinal fistula.
Conclusion: EBUS guided intratumoral cisplatin for IMHR appears to be safe and effective, and may represent a new treatment paradigm for this patient population.

1. Introduction

Lung cancer remains one of the most prevalent and deadly malignancies worldwide with 1.8 million new cases in 2012. It is responsible for nearly one in five cancer-related deaths (19.4%), or 1.59 million deaths annually worldwide, with a case fatality rate of 0.87 [1,2]. The majority of deaths due to lung cancer are secondary to disease recurrence after initial treatment, irrespective of histology, stage or initial treatment. Recurrent lung cancer has been viewed almost universally fatal secondary to a lack of curative treatment modalities. More importantly, recurrence is often associated with significant patient discomfort

Abbreviations: ITC, intratumoral chemotherapy; IMHR, isolated mediastinal and hilar recurrence; EBRT, External beam radiation therapy; PFS, Progression-free survival; CT, computed tomography; PET, positron emission tomography; EBUS, Endobronchial ultrasound.

* Corresponding author at: Division of Pulmonary, Critical Care, and Sleep Medicine University of Florida, 1600 SW Archer Road–Room M452, Gainesville, FL 32610–0225, United States. Fax: +1 352 392 0821.
E-mail address: Hiren.Mehta@medicine.ufl.edu (H.J. Mehta).

http://dx.doi.org/10.1016/j.lungcan.2015.10.009
0169-5002/

requiring substantial supportive treatment and decreased quality of life, thus limiting the feasibility and benefit of further interventions [3].

In 1982, the Radiation Therapy Oncology Group reported an incidence of 34% for locoregional recurrence and 16% for locoregional plus distant failure for NSCLC after irradiation [4]. Although tumor control has improved since then with improved techniques and increases in the dose delivered, there remains a high incidence of local failure after radiotherapy [5,6]. Treatment options for locoregionally recurrent lung carcinomas are limited. The objective response rate of second-line systemic chemotherapy is reported at 10% [7,8]. A recent review concluded that while repeat chest irradiation with EBRT is feasible, most studies in the review focused on symptom relief and palliation rather than disease control [3].

At the University of Florida (UF), we have treated patients with isolated mediastinal and hilar recurrence (IMHR) accessible through bronchoscopy with endobronchial ultrasound (EBUS) guided transbronchial intratumoral injection of cisplatin, with or without concurrent treatment with systemic chemotherapy and/or EBRT. Studies have shown that intratumoral chemotherapy (ITC) is safe, feasible, and effective at debulking of airway tumors [9,10]. Hohenforst-Schmidt et al. demonstrated that ITC in mediastinal nodes can be delivered safely [11], however there is limited to no data regarding its use for disease control for IMHR. The aim of the present work was therefore to study the effectiveness, safety, and feasibility of ITC with cisplatin for isolated mediastinal and hilar recurrences We also analyzed our data to determine whether ITC has any effect on overall survival and/or progression-free survival (PFS). This report describes our institutional experience and management standard for regional failures.

2. Methods and materials

2.1. Patient eligibility and data acquisition

Between January 2009 and September 2014, all patients treated with ITC for IMHR were reviewed. The institutional review board at the University of Florida approved this study (#IRB201400823). All data was prospectively collected and retrospectively analyzed. Patients were enrolled if they satisfied all the following criteria: age 18–80 years, pathologically confirmed NSCLC or small cell lung carcinoma (SCLC), and lung cancer recurrence after definitive EBRT to the site considered for treatment. All patients included in our study had received full dose EBRT to hilar and mediastinal structures at least 6 months before intratumoral therapy was administered. In addition, all recurrences were confirmed by histologic or cytologic examination. Only patients with recurrences limited to the hilar, mediastinal, and peribronchial structures (lymph nodes, nodules, and masses), without evidence of distant metastases, were considered for treatment with ITC. Each patient was restaged with diagnostic computed tomography (CT) of the chest and positron emission tomography (PET)/CT imaging. Each patient was presented at multi-disciplinary thoracic oncology tumor board for their IMHR and considered to have very limited therapeutic options. In all patients, the treatment goal was disease control, with or without palliation of symptoms. All patients were followed with a chest CT or a PET/CT scan 8–12 weeks after the last treatment session to evaluate response. Subsequent follow-up and imaging was completed at the discretion of the patient's treating oncologist. Detailed chart review was performed for all patients to evaluate for toxicity, locoregional recurrence, distant recurrence, PFS, and mortality. For the purposes of this study, local recurrence was defined as the recurrence at the site of treatment and regional recurrence was defined as recurrence in the mediastinum, hilum or supraclavicular fossa. Other sites of recurrence, including contralateral lung and metastatic lymph nodes in the neck or axilla, were defined as distant recurrence.

The primary outcome was response to treatment as measured on repeat CT Chest or PET scan done 8–12 weeks after the final session of intratumoral 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 criteria as described in Table 1 [12]. For purposes of statistical analysis, we classified patients as "responders" (those with CR and PR) and "non-responders" (those with SD and or PD). We evaluated overall survival and PFS in all patients after the final session of ITC, and whether responders had better overall survival as compared to non-responders. We strictly evaluated each patient's first encounter with ITC. Survival (both overall and PFS) were measured from the completion of their first encounter with ITC. Some patients were treated later, but these represent a biased subset (as we believe that patients who had good response to first encounter were the ones more likely to undergo subsequent encounters) and those sites were not included in any analysis for the purposes of this study. Secondary outcomes included response based on tumor histology, size of recurrence, and concurrent systemic therapy. We also measured safety outcomes and feasibility and report them here as secondary outcomes.

2.2. Procedural considerations and technical aspects

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, was used for ITC. The procedure was performed under moderate sedation. Monitoring, local anesthesia, and oxygenation were performed as with standard bronchoscopy. Once the target lesion was located, a 22 gauge EBUS needle, which is housed in a sheath, was advanced through the working channel of the scope and locked in position. Under real time ultrasound guidance, the tracheobronchial wall was punctured and the needle placed in the target lesion. The stylet within the needle was removed and cisplatin was then injected into the lesion. Each site was accessed one to four times at different locations to facilitate injection of the medication throughout. The needle was then retracted back into the sheath. One to two sites were treated per session. Patients recovered per hospital protocol and were discharged home on the same day.

In this study, cisplatin (aqueous solution at a concentration of 1 mg/ml) was used for ITC with a maximal dose of 40 mg per session based on previous published literature [13,14]. The lyophilized cisplatin powder was dissolved in 0.9% NaCl solution just before use. Each site was treated with one to four punctures per session, depending on the size and location of the lesion. If more than one site was treated per session, each site was injected with 20 mg of cisplatin with total dose per session not to exceed 40 mg. A single encounter of ITC consisted of 4 weekly sessions during a 3-week period (on days 1, 8, 15, and 22). Patients were given 10 mg of dexamethasone intravenously as well as 8 mg of ondansetron intravenously at the beginning of the procedure to prevent nausea.

Some patients treated with ITC experienced an isolated recurrence several months later in a different mediastinal or hilar site (separate from the previously treated IMHR) and subsequently underwent another 4 sessions of therapy with ITC. Those patients were classified as having second or subsequent ITC encounters. Once treated, a particular site was never considered for retreatment with ITC on subsequent encounters.

Please cite this article in press as: H.J. Mehta, et al., Treatment of isolated mediastinal and hilar recurrence of lung cancer with bronchoscopic endobronchial ultrasound guided intratumoral injection of chemotherapy with cisplatin, Lung Cancer (2015), http://dx.doi.org/10.1016/j.lungcan.2015.10.009