BRIEF REPORT

Initial Safety and Feasibility Results From a Phase 1, Diagnose-and-Treat Trial of Neoadjuvant Intratumoral Cisplatin for Stage IV NSCLC

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ABSTRACT

Neoadjuvant intratumoral cisplatin has the potential to generate substantial cytotoxicity and immune priming within the tumor environment, while minimizing systemic, off-target, adverse events. We initiated a phase 1A, 3+3 dose-ranging study of neoadjuvant, intratumoral cisplatin, delivered through endobronchial ultrasound bronchoscopy, in the same procedure as the initial diagnosis. There were no dose-limiting toxicity identified at the 20mg level

Keywords: Intratumoral therapy; Cisplatin; Endobronchial ultrasound-guided transbronchial needle injection; Lung cancer

Introduction

Standard-of-care therapy for stage IV NSCLC frequently includes immune checkpoint inhibitor. In patients whose tumor harbors low programmed death-ligand 1 expression, the addition of chemotherapy including either carboplatin or cisplatin (cis-diamminedichloroplatinum) results in better response rates versus immune checkpoint inhibitor alone.[1] Despite this improvement in efficacy,[2] intravenous administration of platinum agents results in significant off-target adverse effects that are synergistically amplified when these agents are used in combination with immunotherapy.[3]

Recently, endobronchial ultrasound-guided transbronchial needle injection (EBUS-TBNI) of cisplatin has arisen as a salvage therapy for patients who previously failed radiation to the target lesion and are not on concomitant systemic cytotoxic therapy.[4–6] Nevertheless, intratumoral cisplatin has not been investigated as first-line therapy for stage IV NSCLC. We initiated a phase 1A, 3+3 dose-ranging study of neoadjuvant, intratumoral cisplatin, delivered through EBUS-TBNI, during the same procedure as the initial diagnosis.

Materials and Methods

Given the novel application of both the EBUS needle and cisplatin, this study required approval by both the University of Vermont (UVM) Committee on Human

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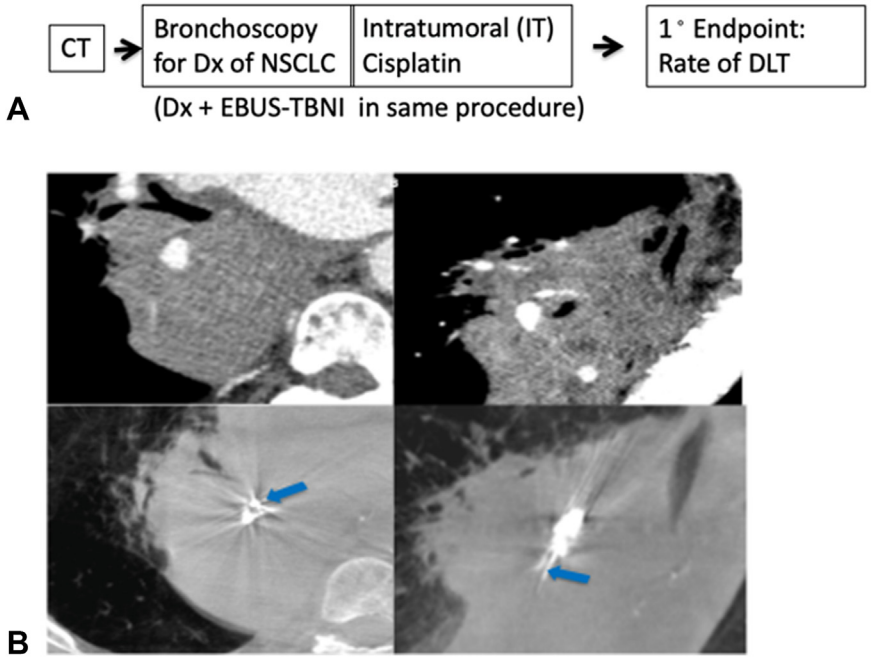

Figure 1. (*A*) Trial schema. (*B*) Axial and coronal preoperative CT (*A*, *B)* and intraoperative cone-beam CT *(C*, *D)* images. Blue arrow denotes the EBUS needle within the lesion. CT, computed tomography; EBUS-TBNI, endobronchial ultrasound-guided transbronchial needle injection; DLT, dose-limiting toxicity; DX, diagnosis.

Research in the Medical Sciences (UVM 00000613) and the Food and Drug Administration (IND 146109). All participants signed informed consent, consistent with the Declaration of Helsinki principles. Eligibility criteria included the following: age above or equal to 18 years, EBUS-accessible primary tumor target, Eastern Cooperative Oncology Group performance status less than or equal to 2, suspected stage IV NSCLC after multidisciplinary review, leukocytes greater than or equal to 3000/mcL, platelets greater than or equal to 100,000/mcL, total bilirubin less than or equal to institutional upper limit of normal, aspartate transaminase (serum glutamic-oxaloacetic transaminase)/alanine transaminase serum glutamic pyruvic transferase) less than or equal to institutional upper limit of normal, and glomerular filtration rate greater than or equal to 60 mL/min/1.73 m^2. Potential cases were reviewed in the UVM Lung Multidisciplinary Clinic (MDC) before the procedure. MDC consensus of stage IV disease (if NSCLC was confirmed during the procedure) and review of other possible clinical trial eligibility (e.g., phase 3 studies) that would be prioritized were obtained before the procedure for all patients. On the procedure day, EBUS was first used to obtain tissue aspirates for rapid on-site cytopathologic evaluation (ROSE). Following confirmation of NSCLC through ROSE and acquisition of all clinically required tissue, intratumoral delivery of cisplatin was performed as described previously (Fig. 1*A*).[4–6] Briefly, the 19G EBUS needle (Olympus Vizishot, Olympus America) is inserted into the lesion under EBUS guidance. Nevertheless, endobronchial ultrasound only provides a two-dimensional view. To insure accurate needle placement in the centroid of the lesion, cone-beam computed tomography is used to confirm positioning (Fig. 1*B*). A single injection of cisplatin (20 mg, 1 mg/mL, Fresenius Kabi) is then administered under real-time EBUS. The airway is then monitored under white-light bronchoscopy for any evidence of extravasation of the agent. Platinum blood levels are obtained at 5, 15, 30, 60, and 120 minutes after injection. Participants are screened for predefined adverse events, as defined by the National Cancer Institute Cancer Therapy Evaluation Program (https://ctep.cancer.gov/protocoldevelopment/sideeffects/drugs.htm) at 24 hours, 1 week, and 2 weeks post-delivery, with safety monitoring laboratories drawn at the 1-week and 2-week time points. Any adverse events greater than or equal to grade three Common Terminology Criteria for Adverse Events are considered dose limiting.

Results

All three participants in the dose cohort were men with ages ranging from 63 to 76 years. Primary target lesions and demographics are listed in Table 1. Cone-beam computed tomography identified the need for EBUS needle repositioning in two cases, with subsequent delivery into the centroid of the lesion.

None of the participants experienced a dose-limiting toxicity. One patient experienced a grade 1, possibly

Table 1. Characteristics of the Cohort

Patient	Age	Sex	Smoking	Treated Location	Histology	Volume (mL)	DLT
1	69	Male	Former	Left hilum	AdenoCa	3153.7	None
2	76	Male	Current	Left upper lobe	Squamous	5893.2	None
3	63	Male	Former	Right hilum	NSCLC	1463.9	None

AdenoCa, adenocarcinoma; DLT, dose-limiting toxicity; NSCLC, NSCLC not otherwise specified.

related, anemia at 1 week, which resolved at the 2-week time point without intervention. Platinum blood levels are displayed in Table 2. There were no significant changes in the white blood cell counts or differential cell counts pre- and post-delivery. Although not significant, in all three patients, there was a drop in the absolute lymphocyte count (mean 0.41, range 0.16–0.57).

Although all cases underwent review through the UVM Lung MDC before diagnosis and EBUS-TBNI cisplatin delivery, final multidisciplinary review confirmed stage IV NSCLC in all cases. Tumor obtained at the time of diagnosis was analyzed for programmed cell death protein 1 expression, with all tumors demonstrating less than 10% programmed death-ligand 1 tumor proportion score. All three patients went on to receive anti–programmed cell death protein 1 therapy and intravenous platinum-based chemotherapy.

Discussion

EBUS-TBNI is an emerging technique for local delivery of drugs and biologics, including chemotherapy, gene therapy, immunogene therapy, and oncolytic viruses.[7] Our group and that of Mehta et al.[6] have published individually and in a combined series, revealing a 77% complete or partial response of the treated lesion for patients with recurrent lung cancer treated through EBUS-TBNI with doses up to 40 mg.[5] Nevertheless, intratumoral cisplatin has the potential to serve as a potent neoadjuvant, immune-priming agent. In this investigation, we evaluated the safety of neoadjuvant intratumoral cisplatin, delivered at the time of diagnosis, for stage IV NSCLC. In the first dose cohort of three patients, 20 mg did not result in any dose-limiting toxicity. This is consistent with our prior experience and a computationally derived dosing algorithm based on data from treated cases.[8] Peak serum platinum levels after intratumoral delivery were approximately 100-fold less than that typically found after intravenous administration.[9]

Despite these encouraging results, we electively halted the current trial based on clinical data obtained in a separate study. In patients with recurrent lung cancer who underwent up to four EBUS-TBNI cisplatin treatments, all preceded by a tissue biopsy, we found evidence that lower doses of intratumoral cisplatin (mean 13 mg) were associated with dynamic increases in CD8+ T cells within the tumor immune microenvironment whereas higher doses (mean 33 mg) were associated with decreases in CD8+ T cells.[10] In the phase 1A study of neoadjuvant intratumoral cisplatin discussed here, there is no repeat biopsy performed, and thus, we cannot comment on the effect of the drug on the tumor immune microenvironment.

The 3+3 approach to determine a recommended phase 2 dose is a well-accepted trial design and in this case was approved by the Food and Drug Administration. Nevertheless, our recent experience highlights an important limitation of applying this design for evaluation of intratumoral therapies. The recommended phase 2 dose in a 3+3 design is determined using a binary assessment of toxicity, based on the assumption that toxicity and efficacy track together. This design has well-documented limitations when applied to immunotherapy,[11] which may be compounded when an agent is delivered intratumorally. Direct deposition of an agent into the tumor has the potential to uncouple efficacy from off-target systemic effects through generation of high local versus systemic tissue concentrations. Nevertheless, this approach still has the potential to result in untoward effects within the tumor microenvironment. In the case of intratumoral cisplatin, the concern is the possibility of lymphocyte toxicity. Unfortunately, there are little data documenting short-term changes in the tumor immune microenvironment, in the time scale of weeks, and it remains unknown whether the T cells within the tumor are repleted from the systemic compartment after platinum-

Table 2. Peak Plasma Platinum Level

Patient	Plasma Level (mcg/L)	Minutes After EBUS-TBNI
1	440	30
2	340	30
3	210	14

EBUS-TBNI, endobronchial ultrasound-guided transbronchial needle injection.

induced decreases. Our recently published data raising the potential for lymphocyte toxicity when recurrent lung cancer is treated with multiple intratumoral cisplatin administrations should be considered hypothesis generating but ethically necessitated that the evaluation of neoadjuvant intratumoral cisplatin be performed in a design that allows assessment of temporal changes in the tumor immune microenvironment.

The phase 1B design, which is also Food and Drug Administration–approved, includes multiple procedures (and biopsies) to temporally evaluate changes in the tumor immune microenvironment over time. The trial schema recapitulates the well-studied treatment course for recurrent disease, which includes up to four weekly procedures. Further phase 1B will test computational predictions that distributing the dose using multiple injections within the tumor is superior to one single injection.[12] The overarching goal of phase 1B is to identify a potential optimal biologic dose through assessments of both adverse events and changes in the tumor immune microenvironment.[13]

In summary, the safety data from this phase 1A study reveal that EBUS-TBNI cisplatin at 20 mg is a potential recommended phase 2 dose. Nevertheless, these data highlight the need for novel trial designs that account for the response of the tumor immune microenvironment. This is also the first study to our knowledge to reveal feasibility of a diagnose-and-treat paradigm for intratumoral therapy, an approach which has the potential to dramatically reduce time-to-treatment for patients with lung cancer.

CRediT Authorship Contribution Statement

Farrah B. Khan: Conceptualization, Methodology, Investigation, Formal analysis, Writing—original draft, Writing—reviewing and editing.

Pamela C. Gibson: Methodology, Investigation, Writing—reviewing and editing.

Scott Anderson: Methodology, Investigation, Writing—reviewing and editing.

Sarah Wagner: Methodology, Investigation, Writing—reviewing and editing.

Bernard F. Cole: Conceptualization, Formal analysis, Writing—reviewing and editing.

Peter Kaufman: Methodology, Investigation, Formal analysis, Writing—reviewing and editing.

C. Matthew Kinsey: Conceptualization, Methodology, Investigation, Formal analysis, Writing—original draft, Writing—reviewing and editing.

Disclosure

Dr. Kinsey has received support from Johnson and Johnson, Nanology, Galvanize Therapeutics and Olympus America and holds patents with Quantitative Imaging Solutions, the University of Vermont and Johnson and Johnson; he holds stock in Quantitative Imaging Solutions and is on the external advisory board on Interventional Oncology of Johnson and Johnson. Dr. Cole has received fees from the Frontier Science and Technology Research Foundation and Insmed and has received payments from the Ipsen EZH302 Study, the Aadi TSC-007n study, BrainStorm Cell Therapeutics, Acrotech Biopharma, CSL Behring, Genentech, GSK and Oncopeptides. The other authors have no funding or relationships to declare.

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Ethics Statement

The study was approved by the by the University of Vermont (UVM) Committee on Human Research in the Medical Sciences (UVM 00000613) and Food and Drug Administration (IND 146109).

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