Surgical Outcomes After Neoadjuvant Chemotherapy and Ipilimumab for Non-Small Cell Lung Cancer

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Background. The objective of this study was to evaluate the safety and feasibility of using neoadjuvant chemotherapy plus ipilimumab followed by surgery as a treatment strategy for stage II-IIIA non-small cell lung cancer.

Methods. From 2013 to 2017, postoperative data from patients who underwent surgery after neoadjuvant chemotherapy plus ipilimumab in the TOP1201 trial, an open label phase II trial (NCT01820754), were prospectively collected. The surgical outcomes from TOP1201 were compared with outcomes in a historical cohort of patients receiving standard preoperative chemotherapy followed by surgery identified from our institution's prospectively collected thoracic surgery database.

Results. In the TOP1201 trial, 13 patients were treated with preoperative chemotherapy and ipilimumab followed by surgery. In the historical cohort, 42 patients received preoperative chemotherapy by a platinum doublet regimen preoperative chemotherapy by a platinum doublet regimen without ipilimumab followed by lobectomy or pneumonectomy. The 30-day mortality in both groups was 0%. The most frequently occurring perioperative complications in the TOP1201 group were prolonged air leak (n = 2, 15%) and urinary tract infection (n = 2, 15%). The most common perioperative complication in the preoperative chemotherapy alone group was atrial fibrillation (n = 6, 14%). One patient (8%) had atrial fibrillation in the TOP1201 group. There was no apparent increased occurrence of adverse surgical outcomes for patients in the TOP1201 group compared with patients receiving standard of care neoadjuvant chemotherapy alone before surgery for stage II–IIIA non-small cell lung cancer.

Conclusions. This report is the first to demonstrate the safety and feasibility of surgical resection after treatment with ipilimumab and chemotherapy in stage II–IIIA non-small-cell lung cancer.

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In recent years, evidence has been published demonstrating that immune therapy can be effective in the treatment of non-small cell lung cancer (NSCLC) [1]. Ipilimumab is a monoclonal antibody that binds the CD28 homolog, CTLA-4, and, in doing so, enhances the costimulation of T cells at their receptor by allowing for binding of CD28 to members of the B7 family on the antigen-presenting cell [2]. In essence, it is believed that in the absence of CTLA-4 interference, T cells that are exposed to their specific antigen may be activated and induce cytotoxicity [3]. In randomized phase II trials, ipilimumab added to carboplatin and paclitaxel improved progression-free survival, overall response, and overall survival in patients with advanced stage IIIB/IV NSCLC [4, 5]. The combination of ipilimumab with nivolumab showed promising activity in a large cohort of patients with untreated stage IIIB/IV NSCLC [6].

The use of immunotherapy agents in either induction or adjuvant therapy for earlier stage NSCLC is currently an important area of investigation. We conducted a single-arm phase II study of the use of neoadjuvant ipilimumab in conjunction with standard chemotherapy for patients with clinical stage IB, II, or III NSCLC—TOP1201—with multiple goals. Although patients with

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clinical stage IB NSCLC were eligible for the study, only patients with clinical stage II to IIIA disease were enrolled. As part of the study, patients who were deemed surgical candidates after induction therapy underwent curative resection. The primary objective of the trial was to evaluate potential immunomodulating effects of ipilimumab on circulating T cells in resected NSCLC. In addition, because very little is known about the effects of immunotherapy agents (eg, ipilimumab) on the rates of postoperative complications, a key secondary goal was to confirm the safety of using induction ipilimumab with chemotherapy. This analysis of safety and feasibility data for surgery after ipilimumab was a prespecified secondary endpoint, and postoperative outcome data were collected prospectively. We report here the analysis of surgical outcome data after neoadjuvant chemotherapy plus ipilimumab followed by surgery for stage II to IIIA NSCLC.

Patients and Methods

Eligible patients were 18 years of age or older with biopsy-proven clinical stage IB, IIA, IIB, or IIIA NSCLC for whom neoadjuvant therapy was considered to be clinically appropriate by our institution's surgical and medical oncology team, although only patients with stage II to IIIA were enrolled in the study. Inclusion criteria included histologic diagnosis of NSCLC, no prior chemotherapy for the current diagnosis of NSCLC, Eastern Cooperative Oncology Group score of 0 or 1, and adequate organ function, positron emission tomography/computed tomography scan, and brain imaging. Each participant signed an Institutional Review Board-approved, protocol-specific informed consent in accordance with federal and institutional guidelines. Patients received neoadjuvant therapy consisting of the following: cycle 1 paclitaxel (175 mg/m^2) with either cisplatin (75 mg/m^2) or carboplatin (area under the curve = 6, capped at 900 mg) without ipilimumab; and cycles 2 and 3 of the same chemotherapy with the addition of ipilimumab (10 mg/kg) on day 1 of each cycle. After the completion of induction therapy, the surgery team assessed surgical eligibility in a multidisciplinary setting. Patients who were not deemed surgical candidates were removed from the trial. At the time of surgery, if participants were found to have bulky residual adenopathy to such a degree that the operation was aborted, they were removed from the protocol. Data were prospectively collected.

The surgical outcomes from this trial were informally compared with outcomes in a cohort of patients receiving standard preoperative chemotherapy followed by surgery identified from an established surgical database. All NSCLC patients at the Duke University Medical Center from 1996 to 2012 who received preoperative chemotherapy with a platinum doublet regimen without ipilimumab followed by lobectomy or pneumonectomy within 12 weeks of completion preoperative chemotherapy were compiled and summarized. These patients were selected based on the use of induction chemotherapy and not by specific cancer stage, which was dependent on physician preference and availability of induction therapy protocols throughout the course of the study. Baseline and outcome variables included demographics, comorbidities, pulmonary function, chest tube duration, length of hospitalization, postoperative bleeding requiring reoperation, postoperative bleeding requiring blood transfusion, pneumonia, prolonged air leak, respiratory failure, other major complications, and overall survival. The use of these patients' data received Institutional Review Board approval with individual patient consent being waived. All analyses comparing outcomes for TOP1201 study patients with outcomes of patients receiving standard neoadjuvant chemotherapy at Duke Medical Center were purely descriptive owing to the small sample size of surgical patients from the TOP1201 trial and the unplanned nature of the comparisons.

Results

Twenty-four eligible patients were enrolled and received neoadjuvant therapy in TOP1201 between March 2013 and December 2015: 3 patients (13%) stage IIA, 2 (8%) stage IIB, and 19 (79%) stage IIIA, with 18 patients (75%) having pretreatment pathologically positive N2 lymph node metastases. The 24 eligible patients had the following characteristics: 12 female (50%), 23 (96%) current or former smokers, 15 (62%) adenocarcinoma, and 9 (37%) squamous cell carcinoma; median age was 65 years. Two patients had a delay in surgery of 4 and 5 weeks, respectively, due to ipilimumab-related diarrhea. Thirteen patients were treated with chemotherapy and ipilimumab followed by surgical resection less than 12 weeks after completion of neoadjuvant therapy.

Most adverse events were those expected for platinum and paclitaxel chemotherapy. Fifty-four percent of patients had a treatment-related grade 1 or 2 adverse event, and 46% had a grade 3 or 4 event, with no treatment-related deaths. Immune-related adverse events considered to be related to ipilimumab were as follows: grade 2 pneumonitis (n = 1, 4%); grade 3 adrenal insufficiency (n = 4, 17%); and diarrhea/colitis (grade 1 or 2, n = 6, 25%; grade 3, n = 3, 13%). Toxicity data are detailed in Supplemental Table 1.

By radiographic Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, criteria, clinical responses after neoadjuvant therapy were as follows: 14 patients (58%) with a partial response; 8 (33%) with stable disease; and 2 (8%) with progression. Median overall survival was 29.2 months (95% confidence interval: 22.1 to not reached), and 24-month overall survival was 73.0% (95% confidence interval: 44.1 to 88.6) for all 24 patients initiating neoadjuvant therapy with ipilimumab. There have been no deaths at 2 years for the patients who underwent surgical resection of their lung cancer.

On assessment after treatment with chemotherapy and ipilimumab, 11 patients were not considered candidates for surgical resection for the following reasons: persistent N2 cancer (n = 5); inadequate pulmonary function (n =

Table 1. Patient and Cancer Characteristics

Characteristics	Preoperative Chemotherapy (n = 42)	Ipilimumab (n = 13)	*p* Value[a]
Sex, no. (%)			0.54
Male	21 (50)	5 (38)	
Female	21 (50)	8 (62)	
Age, years			0.70
Mean ± SD	60.2 ± 10.5	61.4 ± 7.2	
Median (minimum–maximum)	62 (33–76)	59 (51–75)	
Ethnicity, no. (%)			0.76
White	34 (81)	10 (77)	
Black	7 (17)	3 (23)	
Native American	1 (2)	0 (0)	
Histology, no. (%)			0.61
Adenocarcinoma	23 (55)	8 (62)	
Adenosquamous	1 (2)	0 (0)	
Squamous cell carcinoma	10 (24)	5 (38)	
Large cell	3 (7)	0 (0)	
Non-small cell, not otherwise specified	5 (12)	0 (0)	
Clinical stage before chemotherapy, no. (%)			0.88
IB	1 (2)	0 (0)	
IIA	5 (12)	1 (8)	
IIB	5 (12)	2 (15)	
IIIA	26 (62)	10 (77)	
IIIB	1 (2)	0 (0)	
IV	4 (10)	0 (0)	
FEV_1, percent predicted[b]			0.06
Mean ± SD	74.1 ± 20.2	85.9 ± 16.7	
Median (IQR)	76 (55–91)	84 (78–96)	
DLCO, percent predicted[c]			0.08
Mean ± SD	74.1 ± 15.9	82.5 ± 11.2	
Median (IQR)	76 (62–83)	85 (79–90)	
BMI at start of chemotherapy[d], kg/m^2			0.66
Mean ± SD	28.9 ± 5.2	28.2 ± 4.4	
Median (IQR)	28.5 (25.4–31.3)	26.4 (25.3–29.3)	
History of diabetes mellitus, no. (%)	8 (19)	5 (38)	0.26
Renal insufficiency, no. (%)	1 (2)	1 (8)	0.42
Hypertension, no. (%)	22 (52)	6 (46)	0.76
Chronic obstructive pulmonary disease, no. (%)	11 (26)	3 (23)	1.00
Peripheral vascular disease, no. (%)	1 (2)	0 (0)	1.00
Prior thoracic surgery[e], no. (%)	6 (14)	0 (0)	0.32
Congestive heart failure, no. (%)	0 (0)	0 (0)	1.00
Cerebrovascular disease, no. (%)	2 (5)	0 (0)	1.00
Coronary artery disease, no. (%)	5 (12)	5 (38)	0.04
History of smoking, no. (%)			1.00
Yes	37 (88)	12 (92)	
No	5 (12)	1 (8)	
ASA class, no. (%)			0.01
I	1 (2)	0 (0)	
II	25 (60)	2 (15)	
III	15 (36)	9 (69)	
IV	1 (2)	2 (15)	

(*Continued*)

Table 1. Continued

Characteristics	Preoperative Chemotherapy (n = 42)	Ipilimumab (n = 13)	*p* Value[a]
ECOG score, no. (%)			<0.001
0	18 (43)	13 (100)	
1	23 (55)	0 (0)	
2	1 (2)	0 (0)	
Surgical approach, no. (%)			0.003
Open	24 (57)	1 (8)	
Completed VATS	11 (26)	9 (69)	
Converted VATS to open	7 (17)	3 (23)	
Type of resection, no. (%)			0.12
Lobectomy	34 (81)	10 (77)	
Pneumonectomy	8 (19)	1 (8)	
Bilobectomy	0 (0)	1 (8)	
Wedge resection	0 (0)	1 (8)	
Pathologic T status, no. (%)			0.52
T0	6 (14)	2 (15)	
T1a	7 (17)	1 (8)	
T1b	4 (10)	0 (0)	
T2a	14 (33)	4 (31)	
T2b	1 (2)	2 (15)	
T3	8 (19)	4 (31)	
T4	2 (5)	0 (0)	
Pathologic N status, no. (%)			0.37
N0	18 (43)	5 (38)	
N1	13 (31)	2 (15)	
N2	11 (26)	6 (46)	
M stage, no. (%)			0.56
M0	38 (90)	13 (100)	
M1	4 (10)	0 (0)	
Margins of surgical resection, no. (%)			1.00
R0	41 (98)	13 (100)	
R1	1 (2)	0 (0)	
Tumor size, cm			0.67
Mean ± SD	3.1 ± 2.1	3.4 ± 2.4	
Median (minimum–maximum)	2.8 (0–8.5)	3.5 (0–7.8)	
Complete pathologic response, no. (%)	5 (12)	2 (15)	0.66
Downstaged pN2 to pN0, no. (%)	11 (26)	4 (31)	0.73
Downstaged pN2 to pN0 or pN1, no. (%)	14 (33)	5 (38)	0.73

[a] Fisher's exact test *p* values are provided for categoric variables and Student's *t* test *p* values for continuous variables. [b] Forced expiratory volume in 1 second (FEV_1) data only available for 34 of 42 patients in the preoperative chemotherapy group. [c] Diffusion capacity of lung for carbon monoxide (DLCO) data only available for 34 of 42 patients in the preoperative chemotherapy group. [d] Body mass index (BMI) data only available for 23 of 42 patients in the preoperative chemotherapy group. [e] Prior thoracic surgery is defined as any cardiac surgery or lung surgery requiring resection.

Values are n (%) unless otherwise indicated.

ASA = American Society of Anesthesiologists; ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; VATS = video-assisted thoracic surgery.

2); cancer progression (n = 2); location of tumor (n = 1); and preoperative complications leading to the patient not reporting for surgery (n = 1). One of the patients who was excluded owing to inadequate pulmonary function had borderline pulmonary function at initial consideration for the trial (forced expiratory volume in 1 second [FEV_1] = 59%), but it was thought that the neoadjuvant therapy might reduce disease severity and improve pulmonary function before surgery or result in a lesser anatomic resection (lobectomy instead of pneumonectomy). However, at the time of surgery, pulmonary function was unchanged (FEV_1 = 59%), and the tumor remained such that a pneumonectomy was still required, which would have resulted in a predicted FEV_1 of 32% after surgery—still a contraindication to surgery. The other patient who was excluded because of inadequate pulmonary function had borderline pulmonary function at the time of surgery and had had a pulmonary

Table 2. Perioperative Outcomes of Patients Who Received Preoperative Chemotherapy Without Ipilimumab

Characteristics	Preoperative Chemotherapy (n = 42)	Ipilimumab (n = 13)
Thirty-day mortality, no. (%)	0 (0)	0 (0)
Ninety-day mortality, no. (%)	1 (2)	0 (0)
Length of hospitalization, days	5 (4–7)	5 (4–6)
Chest tube duration, days	3 (2–4)	3 (2–5)
Overall complications		
Postoperative bleeding requiring blood transfusion, no. (%)	3 (7)	0 (0)
Perioperative blood transfusions[a], no. (%)	0 (0)	2 (15)
Postoperative bleeding requiring reoperation, no. (%)	2 (5)	0 (0)
Pneumonia, no. (%)	3 (7)	0 (0)
Atrial fibrillation, no. (%)	6 (14)	1 (8)
Prolonged air leaks, no. (%)	4 (10)	2 (15)
Respiratory failure, no. (%)	2 (5)	0 (0)
Urinary tract infection, no. (%)	1 (2)	2 (15)
Vocal cord paralysis, no. (%)	2 (5)	1 (8)
Thromboembolic event, no. (%)	0 (0)	1 (8)

[a] Not from postoperative bleeding.

Values are n (%) or median (interquartile range).

embolism that had not been present at the time of initial inclusion in the trial. The patient who was excluded because of tumor location had a centrally located tumor with N2 disease. It was thought that if there were nodal downstaging in response to neoadjuvant treatment or if the tumor had shrunk enough to not require pneumonectomy, surgery could be beneficial. Although there was good response to treatment, the disease was still present in the N2 lymph nodes, and the tumor was still central and would require pneumonectomy. As it had been decided that doing a pneumonectomy in the setting of N2 disease is not likely to add significant survival benefit over definitive chemoradiation, the patient was excluded from surgery.

Therefore, only 1 of 24 patients did not have surgery owing to adverse events during the neoadjuvant treatment period. Of these 11 patients excluded before surgery, 10 had clinical stage IIIA disease and 1 had clinical stage IIIB disease. Two patients had delay in surgery of 4 and 5 weeks, respectively, due to ipilimumab-related diarrhea. Thirteen patients were treated with chemotherapy and ipilimumab followed by surgical resection within 12 weeks after completion of neoadjuvant therapy (Table 1). All 13 patients underwent mediastinoscopy; 9 patients underwent mediastinoscopy before induction therapy, and 4 patients underwent mediastinoscopy before surgery but after induction therapy.

The Duke Medical Center thoracic surgery database included 42 patients who received preoperative chemotherapy with a platinum doublet regimen as standard of care without ipilimumab followed by lobectomy or pneumonectomy within 12 weeks of preoperative chemotherapy without preoperative radiation. The characteristics of the two groups of patients can be found in Table 1.

The perioperative surgical outcome data from both groups are summarized in Table 2. The statistical design of the trial did not include a formal comparison of the surgical outcome data from the TOP1201 trial with a specific neoadjuvant chemotherapy surgical outcome dataset. However, there was no apparent increased occurrence of adverse surgical outcomes for TOP 1201 patients with chemotherapy plus ipilimumab compared with patients receiving standard of care neoadjuvant chemotherapy alone before surgery for stage II to IIIA NSCLC. The most common perioperative complication in the chemotherapy alone group was atrial fibrillation (n = 6, 14%). One patient (8%) had atrial fibrillation in the chemotherapy plus ipilimumab group. The most frequently occurring perioperative complications in the chemotherapy plus ipilimumab group were prolonged air leak (n = 2, 15%) and urinary tract infection (n = 2, 15%). Two patients in the chemotherapy plus ipilimumab group received blood transfusions during the postoperative period: 1 patient received 1 unit of blood as part of the treatment for vasodilatory shock from the patient's epidural, and another patient received 1 unit of blood as part of the workup and treatment for persistent sinus tachycardia, which later resolved and was thought to be from catecholamine release from surgical stress. There was no evidence of a detrimental effect with the addition of ipilimumab on postoperative overall survival between study patients and standard-of-care neoadjuvant chemotherapy patients.

Comment

In this small study, the use of neoadjuvant ipilimumab with chemotherapy before surgical resection of stage II-IIIA NSCLC was found to be safe and feasible. Preliminarily, there was no apparent increase observed in adverse surgical outcomes in the TOP1201 group when informally compared to the outcomes in a cohort of patients receiving standard preoperative chemotherapy followed by surgery identified from an established single-center surgical database.

Currently, ongoing studies are investigating the use of ipilimumab in immune therapy combination treatments. The combination of ipilimumab and nivolumab has demonstrated efficacy and has been approved as therapy for malignant melanoma [7]. The combination of ipilimumab and nivolumab has also shown promising activity in advanced NSCLC [6]. There is a large randomized trial planned to compare neoadjuvant chemotherapy with nivolumab plus ipilimumab before surgery for early stage NSCLC [8]. Therefore, ipilimumab will continue to be studied in neoadjuvant combinations for early stage NSCLC, and surgical outcome data for neoadjuvant ipilimumab are relevant to ongoing clinical trials of early stage NSCLC.

Based on trials involving melanoma, ipilimumab has a well-characterized side effect profile, some of which,

particularly those involving the gastrointestinal tract, can be severe [9]. In addition, prior reports of adverse events after neoadjuvant treatment with molecular agents has rightly generated interest in what impact ipilimumab may have on the surgical subset in our study. Our investigators anticipated that surgical outcome data after ipilimumab in NSCLC would be of interest, and hence, postoperative data were prospectively collected. As a frame of reference, we included the results from our experience with the surgical management of patients after induction chemotherapy. The perioperative mortality and morbidity for the cohort of patients undergoing standard induction chemotherapy did not differ significantly from the cohort of patients who received ipilimumab followed by surgery. Both groups had 0% 30-day mortality and low rates of major complications. Of note, the inclusion of these data is intended to provide only an informal comparison between the surgical patients from the TOP1201 study and patients who previously had undergone lobectomy after standard induction chemotherapy regimens at our center.

Importantly, the perioperative mortality and morbidity rates in the surgical patients from the TOP1201 trial did not differ significantly from those reported previously in multiinstitutional randomized controlled trials that evaluated the outcomes of patients undergoing preoperative chemotherapy followed by surgery versus surgery alone for NSCLC [10–15]. The 0% 30-day mortality seen in TOP1201 is similar to the 0% to 7% postoperative mortality rate previously reported [10–12, 14, 15]. The percentage of patients with atrial fibrillation was 8% in TOP1201, which is consistent with previously reported results of 5% to 16% [10, 15]. No patients in the TOP1201 group had pneumonia or respiratory failure, whereas the previously reported rate of pneumonia and respiratory failure in randomized trials was 6% to 10% [10, 12, 13] and 7% [10], respectively. Specifically comparing the perioperative mortality and morbidity rates from the TOP1201 trial with that of the Southwest Oncology Group Trial S9900 [10], we found comparable rates of pneumonia (0% versus 7%) reintubation (0% versus 7%), chest tube air leak (15% versus 9%), respiratory failure (0% versus 7%), and atrial fibrillation (8% versus 16%). In summary, the cohort of patients who underwent surgery after ipilimumab in TOP1201 did not have postoperative complications outside the range of what has previously been reported for neoadjuvant chemotherapy alone, suggesting that surgery can be safely performed after the administration of ipilimumab.

This is a small study, and it is possible that we would have seen more treatment-related complications with a larger patient cohort. Nevertheless, this report is the first to demonstrate the safety of surgical resection after treatment with ipilimumab in stage II to IIIA NSCLC. Given that this drug and others like it continue to be studied both individually and in combination, these findings have a particular pertinence to the general thoracic oncology community, for oncologists and thoracic surgeons alike.

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