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Original Article

Multicenter phase 2 study of intrapleural nivolumab in patients with metastatic non-small cell lung cancer and pleural effusion

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Abstract: About 40% of patients with non-small cell lung cancer (NSCLC) developed pleural effusions at some time during the course of their disease. Preliminary results from our Phase 2 multicentre clinical trial (Cohort 1) demonstrated the safety of intrapleural nivolumab in cancer patients. In Cohort 2 we assessed the preliminary efficacy and toxicity of intrapleural instillation of the nivolumab in patients with metastatic NSCLC and large pleural effusion requiring evacuation. Thoracentesis followed by nivolumab (40 mg, single intrapleural instillation) was performed. The primary endpoint was 3-month recurrence-free survival. Simon's two-stage design was used, with 13 patients planned for stage 1. If 11 or more patients did not have a pleural effusion after 3 months, an additional 35 patients were planned to be accrued for a total of 48. A total of 13 patients were enrolled. This study did not meet its primary endpoint and was terminated. Eight patients (61.5%) had a recurrence of pleural effusion at 3 months. The median time to recurrence was 1.84 months (95% CI 1.19-2.49). No adverse events were identified. We concluded that a single intrapleural instillation of the nivolumab at 40 mg was ineffective and well-tolerated in patients with metastatic NSCLC and pleural effusion.

Keywords: Nivolumab, intrapleural instillation, malignant pleural effusion, metastatic non-small cell lung cancer

Introduction

About 40% of patients with non-small cell lung cancer (NSCLC) developed pleural effusions at some time during the course of their disease [1]. Malignant pleural effusion has long been recognized as a poor risk factor and patients have inferior overall survival with median of 3-12 months [2-4]. Pleural effusion does not only have an impact on survival but also cause a huge repercussion on a patient's quality of life [5].

In accordance with current approaches, conservative treatment is recommended, including local treatment (pleurodesis or catheter drainage) followed by systemic therapy [4, 6]. Unfortunately, patients with malignant pleural effusion, especially those requiring pleural evacuation, experienced poorer local control and survival when treated with immunotherapy [7]. The pleura could act as a natural barrier that can limit the penetration of immune checkpoint inhibitors [7, 8].

We have previously demonstrated the safety of intrapleural nivolumab in patients with metastatic renal cell carcinoma and NSCLC (Cohort 1) [9]. In this pilot phase 2 study (Cohort 2), we assessed the preliminary efficacy and toxicity of intrapleural instillation of the nivolumab in patients with metastatic NSCLC and large pleural effusion requiring evacuation.

Methods

This open-label, phase 2 trial was done at four centers. In Cohort 2, patients were adults with squamous or nonsquamous stage IV or recurrent NSCLC, Eastern Cooperative Oncology

Table 1. Patient and disease characteristics

	N=13
Median age, years (range)	66.3 (31-86)
Sex, N (%)	
Male	8 (61.5)
Female	5 (38.5)
Histological subtype of NSCLC, N (%)	
Squamous cell	7 (53.8)
Adenocarcinoma	6 (46.2)
ECOG PS, N (%)	
1	5 (38.5)
2	6 (46.1)
3	2 (15.4)
Visceral metastases, N (%), including	13 (100)
Lung	12 (92.3)
Lymph nodes	9 (69.2)
Liver	9 (69.2)
Bone	4 (30.8)
Adrenal	1 (7.7)
Brain	1 (7.7)
Pleural carcinomatosis confirmed by CT scan, N (%)	10 (76.9)
Volume of pleural fluid, L, median	1.2
Systemic therapy for metastatic disease, N (%)	
Pembrolizumab, first-line	8 (61.5)
Nivolumab + Ipilimumab, first-line	4 (30.8)
Atezolizumab, bevacizumab, chemotherapy, third-line	1 (7.7%)

Group (ECOG) performance-status score of 0-3, and cytologically confirmed malignant pleural effusion, who had a large fluid volume (>1 L) and required evacuation. An additional key inclusion criterion was systemic therapy with a checkpoint inhibitor (monotherapy or combination with another checkpoint inhibitor). We excluded patients if they had presence of EGFR mutations or known ALK translocations sensitive to targeted therapy, autoimmune disease, untreated symptomatic central nervous system metastases or previous therapy with intrapleural instillations. The study protocol and informed consent were approved by the institutional review board. The study was done in accordance with the Declaration of Helsinki, and applicable local regulatory requirements and laws. Patients provided written informed consent before study initiation.

All thoracenteses were performed under ultrasonography guidance. Pleural pressures were measured by a simple water manometer as described [10]. After thoracentesis, a single intrapleural instillation of nivolumab 40 mg diluted in 40 ml of sodium chloride solution (0.9%) was performed. Efficacy was assessed, using computed tomography scan, at baseline (screening), weeks 5, 9, 13, and every 8 weeks thereafter. We assessed adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

The primary endpoint reported here is investigator-assessed 3-month recurrence-free survival defined as the proportion of pleural effusion-free (<200 mL) patients at 3 months. Secondary endpoints included the rate of any grade adverse events and the time to recurrence. Simon's two-stage design was used, with 13 patients planned for stage 1. If 11 or more patients had no recurrence of pleural effusion after 3 months, it was planned to enroll an additional 35 patients, for a total of 48. This design yields a type I error rate of 0.05 and power of 0.8 when the true recurrent-free rate is 90% and the null hypothesis is 75% [11]. Descriptive statistics (mean, median, and proportion) were used to summarize baseline patient characteristics and treatment features. Survival was analyzed using the Kaplan-Meier method. All statistical analyses were carried out using IBM SPSS Statistics Base v22.0 (SPSS, Inc., Chicago, IL, USA).

Results

From August 2020 through September 2022, a total of 13 patients were enrolled in Cohort 2. The median age at diagnosis was 66.3 years (range, 31 to 86 years); 46.2% of patients were older than 70 years. Most of the patients were male (N=8, 61.5%). All patients had visceral metastases, and 10 patients (76.9%) had confirmed pleural carcinomatosis (**Table 1**). Of the 12 patients who had a PD-L1 expression level of 1% or more, 8 were assigned to receive pembrolizumab monotherapy and 4 to receive nivolumab plus ipilimumab in first-line setting.

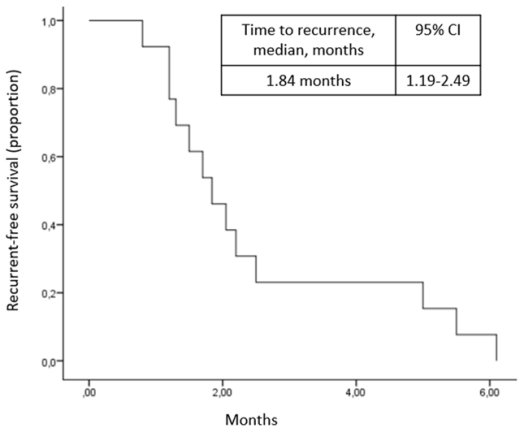

Figure 1. Recurrent-free survival (Kaplan-Maier curve).

One patient received third-line therapy with atezolizumab, bevacizumab, and chemotherapy.

The study did not meet its primary endpoint and was terminated after stage 1 because the intended efficacy was not observed. Five (38.5%) patients had no pleural effusion and 8 patients (61.5%) had relapse at 3 months. Recurrence was found in 2 of 5 patients (40%) with initial response to intrapleural nivolumab. All of these patients underwent ambulatory small catheter drainage with median fluid volume of 0.9 L. Thirteen (100%) patients had no relapse, dyspnea or cough within first month, and the median time to recurrence was 1.84 months (95% confidential interval (CI) 1.19-2.49; **Figure 1**). Three (23.1%) patients had no pleural fluid at 5 months.

Four of 8 patients (50%) with pleural effusion recurrence had distant progression of cancer including local progression (new pleural lesions, n=3, 37.5%). Three of 5 patients (60%) with no recurrence of pleural effusion had also distant progression. However, there were no new pleural metastases in this subgroup. The median overall survival was 12.1 months (95% CI 7.0-17.4).

No any adverse events of intrapleural instillation of nivolumab were identified.

Discussion

To our knowledge, this is the first study that has evaluated the preliminary efficacy of intrapleural checkpoint inhibitors. Our hypothesis was to activate the immune environment of the pleural space using nivolumab and influence the complex interaction of tumor and immune cells. There have been several studies evaluating the efficacy of intrapleural administration of cytokines including interferon gamma [12], interferon α2b [13], and interleukin-2 (IL-2) [14, 15]. Intrapleural IL-2 was well tolerated by patients with NSCLC, but traditionally the efficacy was low. In addition, levels of IL-2 administered intrapleurally were significantly higher than in plasma, assuming that locally administered protein is isolated in the pleural cavity [16]. It can be assumed that large molecule biologics, such as antibodies, will have a similar concentration when injected directly into the pleura.

However, we did not observe preplanned efficacy of the direct instillation of nivolumab into the pleural space. Two thirds of patients had a relapse at 3 months. Thus, study was terminated after stage 1 and patient recruitment was stopped. On the other hand, all patients had local control during first month and median time to recurrence was 1.84 months. We can suppose that multiple installations of nivolumab may be more effective. The dose of the antibody can also affect effectiveness. For example, intravenous nivolumab is used monthly at a dose of 480 mg, which is 12-fold higher than in our study. Other limitations of this study included non-randomized design and different options of systemic therapy.

In conclusion, single intrapleural instillation of the nivolumab at 40 mg was ineffective in patients with metastatic NSCLC and large pleural effusion. Intrapleural irrigation was well tolerated in all patients.

Disclosure of conflict of interest

None.

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