Translational Oncology
www.transonc.com

Volume 7 Number 2 April 2014 pp. 303–308 303

Percutaneous Fine-Needle 5% Ethanol-Cisplatin Intratumoral Injection Combined with Second-Line Chemotherapy Improves On the Standard of Care in Patients with Platinum-Pretreated Stage IV Non–Small Cell Lung Cancer[1]

Qi Niu*, Wei Wang*, Qian Li†, Yong Li*, Douglas M. Ruden‡ and Baoming He§

*Department of Medical Oncology, No. 309 People's Liberation Army Hospital, Beijing, People's Republic of China; †Department of Internal Medicine, Beijing Language and Culture University Hospital, Beijing, People's Republic of China; ‡Department of Obstetrics and Gynecology, Institute of Environmental Health Sciences, CS Mott Center for Human Health and Development, Wayne State University, Detroit, MI, USA; §Department of Radiology, No. 309 People's Liberation Army Hospital, Beijing, People's Republic of China

Abstract

BACKGROUND: Efficacy of second-line chemotherapy in platinum-pretreated non–small cell lung cancer (NSCLC) is poor. This study investigated efficacy of computed tomography–guided percutaneous fine-needle 5% ethanol-cisplatin intratumoral injection (CT-PFNECII) combined with second-line chemotherapy in patients with platinum-pretreated stage IV NSCLC. *PATIENTS:* Between October 2011 and July 2013, 34 eligible patients were randomly assigned to receive either CT-PFNECII combined with second-line chemotherapy (combination group, $n = 17$) or second-line chemotherapy alone (chemotherapy group, $n = 17$). The primary end points were the proportions of patients who achieved an overall response rate (ORR) and disease control rate (DCR). Secondary end points were median survival and progression-free survival (PFS). *RESULTS:* The ORR and DCR in the combination group were significantly higher than in the chemotherapy group (23.53% *vs* 11.76% for ORR, $P < .01$; and 58.82% *vs* 35.29% for DCR, $P < .01$). Compared with patients in the chemotherapy group, patients in the combination group had significantly longer PFS (5.4 months *vs* 3.0 months, $P < .01$) and median survival (9.5 months *vs* 5.3 months, $P < .01$). *CONCLUSIONS:* CT-PFNECII combined with second-line chemotherapy provided a higher response rate and improved survival than second-line chemotherapy for patients with platinum-pretreated stage IV NSCLC.

Translational Oncology (2014) 7, 303–308

Introduction

Lung cancer is the most common cancer in the world, and non–small cell lung cancer (NSCLC) accounts for approximately 80% of all cases of lung cancer. Platinum-based chemotherapy is the standard first-line care for NSCLC [1,2]. However, platinum resistance and tumor recurrence, which are believed to be mediated by cancer stem-like cells (CSCs) or side-population cells, invariably develop [3–5]. Currently, second-line chemotherapy is the standard of care for platinum-pretreated NSCLC even though its efficiency is poor [1,2,5].

Docetaxel and pemetrexed are currently the standard second-line chemotherapy agents for NSCLC. Treatment with pemetrexed generally results in clinically equivalent efficacy outcomes with docetaxel in the second-line treatment of patients with advanced NSCLC [1]. However, pemetrexed and docetaxel only produced overall response rates (ORRs) of 9.1% and 8.8% with a median survival time of 8.3 and 7.9 months, respectively, in platinum-pretreated NSCLC [1].

Address all correspondence to: Qi Niu, MD, PhD, Department of Medical Oncology, No. 309 People's Liberation Army Hospital, Beijing 100091, People's Republic of China. E-mail: qi_niu@hotmail.com

[1] The project was supported by the Scientific Research Foundation for the Returned Overseas Chinese Scholars, China State Education Ministry (No. 2007–1108) to Q.N.
Received 23 September 2013; Revised 23 September 2013; Accepted 11 February 2014

1936-5233/14 http://dx.doi.org/10.1016/j.tranon.2014.02.017

The epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) erlotinib and gefitinib have also been used as standard second-line agents in treating NSCLC. Sensitivity to EGFR TKIs is dependent on the activation of the EGFR pathway or the presence of EGFR-interacting proteins [5]. Studies showed that no significant differences in efficacy were noted between patients treated with TKIs and those treated with docetaxel or pemetrexed in platinum-pretreated NSCLC [5–7].

Therapeutic inhibition of EGFR with TKIs has resulted in favorable response rates only in 11.14% to 15.25% of platinum-pretreated NSCLC, mostly because the *EGFR* mutation or gene amplification rate is only 16.6% in NSCLC [5,6]. In addition, median survival of 7.6 months for gefitinib in platinum-pretreated NSCLC and 5.3 months for erlotinib in platinum-resistant NSCLC indicate the desperate need for novel approaches to treat the patient population [5,7–9].

We previously found that 5% ethanol-cisplatin injected intratumorally could eradicate cisplatin-resistant lung tumors and extend survival by improved killing of lung CSCs in mice [10]. We believe that 5% ethanol improves the efficacy of CSC killing by inhibiting breast cancer resistance protein (BRCP/ABCG2) drug transporter function and by improving the penetration of cisplatin into the tumor cells [10]. On the basis of our model organism studies, it is possible that computed tomography (CT)–guided percutaneous fine-needle 5% ethanol-cisplatin intratumoral injection (CT-PFNECII) might also regress platinum-pretreated or even platinum-resistant tumors in patients with NSCLC by killing chemoresistant cancer stem cells and cancer cells. Furthermore, it is possible that the residual unkilled but damaged tumor cells after 5% ethanol-cisplatin treatment might be more fragile and sensitive to systemic second-line chemotherapy agents. Thus, combination of CT-PFNECII with systemic second-line chemotherapy might provide a new way to improve survival of this patient population.

This study is aimed to investigate the efficacy and safety of CT-PFNECII combined with second-line chemotherapy in patients with platinum-pretreated stage IV NSCLC.

Patients and Methods

Patients

The study protocol was approved by the Institutional Review Boards of the No. 309 People's Liberation Army Hospital in Beijing, and the study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Adult patients with histologically documented NSCLC who received ≥1 platinum-based chemotherapy regimen, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, were potentially eligible for this study. Patients were excluded if they had a life expectancy of less than 1 month or had an indication for liver, renal, or heart failure. Thirty-four eligible patients were enrolled in this study and asked for written informed consent. Information collected at baseline included sex, age, ECOG performance status, tumor size, histology, disease stage, lung tumor–related chest pain or dyspnea, time since last chemotherapy (interval from last chemotherapy to inclusion), times of CT-PFNECII, and platinum resistance. Protocol design, data collection, and analysis were solely the responsibility of the authors.

Study Design

Eligible patients were randomly assigned to receive either CT-PFNECII combined with second-line chemotherapy (standard pemetrexed or docetaxel dosing schedule) (combination group, n = 17) or second-line chemotherapy (standard pemetrexed or docetaxel dosing schedule) alone (chemotherapy group, n = 17).

If a patient received prior taxane treatment, such as docetaxel or paclitaxel, pemetrexed was given as second-line chemotherapy. Otherwise, docetaxel was given as second-line chemotherapy.

Ethanol-cisplatin (5%) was freshly prepared with 10 mg (2 ml) of cisplatin (Qilu Pharmaceutical Co, Ltd, Shandong, China) dissolved into an ethanol solution of 20 to 30 ml with the final ethanol concentration of 5% (vol/vol). Next, the freshly prepared 20 to 30 ml of 5% ethanol-cisplatin solution was percutaneously injected into the lung tumor individually with a 22-gauge fine needle (Gallini Medical Devices, Via Frattini, Italy) under CT (GE Healthcare, Waukesha, WI) guidance, once a week. This procedure was performed weekly for two consecutive weeks, and a third week with no treatment completed one cycle. Single chemotherapy agent pemetrexed (Alimta; Eli Lilly and Company, Indianapolis, IN) (500 mg/m^2 as a 10-minute IV infusion on day 1 of a 21-day cycle) or docetaxel (Taxotere; Aventis Pharmaceuticals, Bridgewater, NJ) (75 mg/m^2 as a 1-hour IV infusion on day 1 of a 21-day cycle) was administered IV 1 day after CT-PFNECII every 3 weeks as a cycle. Each patient in the combination group received one to two cycles of CT-PFNECII and four cycles of pemetrexed/docetaxel, and each patient in the chemotherapy group received four cycles of pemetrexed/docetaxel. Patients on the pemetrexed arm were instructed to take folic acid (350-1000 μg) orally daily beginning approximately 1 to 2 weeks before the first dose of pemetrexed and continuing daily until 3 weeks after the last dose of pemetrexed. A 1000-μg vitamin B12 injection was administered intramuscularly 1 week before the first dose of pemetrexed and was repeated approximately every 9 weeks until after discontinuation. Patients on the pemetrexed arm were instructed to take dexamethasone (Guizhou Guangzheng Pharmaceuticals, Guizhou, China) (4 mg orally twice daily the day before, the day of, and the day after pemetrexed) as a prophylactic measure against skin rash. Patients on the docetaxel arm were instructed to take dexamethasone (8 mg orally twice daily the day before, the day of, and the day after docetaxel).

Follow-up and Study End Points

All patients were followed up every 2 months regularly after the treatment protocol was finished. Patients were evaluated and followed up with ORR, disease control rate (DCR), progression-free survival (PFS), median overall survival (OS), and safety profile. Responses were assessed with the use of the Response Evaluation Criteria in Solid Tumors (RECIST, set by an international collaboration including the European Organisation for Research and Treatment of Cancer, National Cancer Institute of the United States, and the National Cancer Institute of Canada Clinical Trials Group), and toxic effects were assessed according to the Common Toxicity Criteria of the National Cancer Institute (Bethesda, MD) (version 2.0). Lung tumor–related symptoms including chest pain and dyspnea before and after CT-PFNECII were observed. CT-PFNECII–related side effects including pain, cough, fever, hemoptysis, and pneumothorax and chemotherapy-related side effects including myelosuppression and gastrointestinal reaction were observed in this study.

All patients were followed up until death or until the end of the study, with a minimum of 2 months and maximum of 18 months of follow-up.

Statistical Analysis

All primary analyses were performed on an intention-to-treat principle. The RECIST analysis was calculated according to the