Observational Study

Medicine®

OPEN

Icotinib and whole-brain radiotherapy for the treatment in patients with brain metastases from EGFR-mutant nonsmall cell lung cancer

A retrospective study

Ai-Ying Jiang, MM[a], Jing Zhang, MD[b], Hai-Long Luo, MM[c], Feng Gao, MB[d], Yu-Feng Lv, MM[a,*]

Abstract

This study aimed to explore the effect and toxicity of icotinib and whole-brain radiotherapy (IWBRT) for the treatment of brain metastases from nonsmall cell lung cancer (BMNSCLC) with epidermal growth factor receptor (EGFR)-mutant among Chinese Han population.

A total of 55 patients with EGFR-mutant BMNSCLC were included. They received orally icotinib (125 mg/tablet, 125 mg each time, 3 times daily) until disease progression. In addition, they also underwent whole-brain radiotherapy (3-Gy fractions once daily, 5 days weekly for a total dose of 30 Gy) in an attempt to extend their survival time. The outcomes consisted of complete response (CR), partial response (PR), stable disease (SD), progress disease (PD), overall response rate (ORR), progression-free survival (PFS), and overall survival (OS). In addition, toxicity was also recorded in this study.

The CR, PR, SD, PD, ORR, PFS, and OS were 38.2%, 52.8%, 5.4%, 3.6%, 90.1%, 12.5%, and 48.0% months, respectively. In addition, mild toxicity was observed in this study.

This study demonstrated that IWBRT is efficacious with acceptable toxicity for patients with EGFR-mutant BMNSCLC among Chinese Han population.

Abbreviations: BMNSCLC = brain metastases from nonsmall cell lung cancer, CR = complete response, CSF = cerebrospinal fluid, EGFR = epidermal growth factor receptor, EGFR-TKIs = EGFR tyrosine kinase inhibitors, IWBRT = icotinib and whole-brain radiotherapy, NSCLC = nonsmall cell lung cancer, ORR = overall response rate, OS = overall survival, PD = progress disease, PR = partial response, WBRT = whole-brain radiotherapy.

Keywords: brain metastases, effect, icotinib, nonsmall cell lung cancer, toxicity, whole-brain radiotherapy

1. Introduction

Lung cancer is one of the most common conditions in the respiratory diseases. It is also the most cause of cancer-related death around the world.[1–3] Of this, nonsmall cell lung cancer (NSCLC) accounts for 80% to 85% of the whole lung cancers.[4,5] It has been reported that among patients with NSCLC, approximately 20% to 40% may develop brain metastases.[6,7]

Several treatment strategies are used to treat such condition, including medication combination,[8–12] whole-brain radiotherapy (WBRT),[13,14] stereotactic radiosurgery,[15–17] and surgical resection.[18–20] As for the WBRT, the median survival time of patients with brain metastases from nonsmall cell lung cancer (BMNSCLC) often affect by their ages, the tumors' performance score, numbers, and location of metastatic lesions.

Icotinib, an epidermal growth factor receptor (EGFR) pathway inhibitor, is currently used as a new first-generation EGFR tyrosine kinase inhibitors (EGFR-TKIs).[13,21] Its structure is similar with erlotinib. It utilized for the treatment in patients with NSCLC. Preclinical data have showed that icotinib enhances the efficacy in patients with BMNSCLC, when combined with WBRT.[13,14] In addition, it is also not inferior to the patients with advanced NSCLC by treating with gefitinib.[21]

Presently, limited data of icotinib and whole-brain radiotherapy (IWBRT) for the treatment of EGFR-mutant BMNSCLC among Chinese Han population have been reported. In this study, we retrospectively analyzed the effect and toxicity of IWBRT in patients with EGFR-mutant BMNSCLC among Chinese Han population.

2. Patients and methods

2.1. Ethics

This study was formally approved by the Medical Ethical Committee of the Affiliated Hongqi Hospital of Mudanjiang

Editor: Qinhong Zhang.

The authors have no funding and conflicts of interest to disclose.

[a] Department of Respiratory Medicine, The Affiliated Hongqi Hospital of Mudanjiang Medical University, [b] Department of Anatomy, Mudanjiang Medical University, [c] Department of Neurology, The Affiliated Hongqi Hospital of Mudanjiang Medical University, [d] Department of Anesthesiology, Mudanjiang Hospital of Traditional Chinese Medicine, Mudanjiang, China.

[*] Correspondence: Yu-Feng Lv, Department of Respiratory Medicine, The Affiliated Hongqi Hospital of Mudanjiang Medical University, No. 5 Tongxiang Road, Aiming, Mudanjiang 157011, China (e-mail: lvyf2015@163.com).

Medicine (2018) 97:15(e0312)

Received: 16 October 2017 / Received in final form: 6 March 2018 / Accepted: 9 March 2018

http://dx.doi.org/10.1097/MD.0000000000010312

Table 1

Characteristics of included patients.

Characteristics	Value
Mean age, y	63.1 (12.5)
Sex	
Male	25 (45.5)
Female	30 (54.5)
Ethnicity (Chinese Han)	55 (100.0)
Marital status	
Married	36 (64.5)
Divorced	12 (21.8)
Widowed	7 (12.7)
Karnofsky performance score	
100	2 (3.7)
90	15 (27.3)
80	30 (54.5)
70	8 (14.5)
EGFR mutant	55 (100.0)
Histology	
Large cell carcinoma	11 (0.2)
Squamous cell carcinoma	5 (9.1)
Adenocarcinoma	39 (70.9)
Brain metastases, no.	
≤3	35 (63.6)
>3	20 (36.4)
Smoking status	
History or current	37 (62.3)
Never	18 (37.7)
Extra-cranial metastases	
Absent	23 (41.8)
Present	32 (58.2)

Data are present as mean ± standard deviation or number (%).
EGFR = epidermal growth factor receptor.

Medical University, and the informed consent was obtained from all patients. It was conducted at the Affiliated Hongqi Hospital of Mudanjiang Medical University from January 2011 to December 2013.

2.2. Patients

In this retrospective study, 55 patients with the diagnosis of BMNSCLC by computed tomography or magnetic resonance imaging scan were included. The clinical characteristics of all included patients are showed in Table 1. Patients aged from 31 to 78 years, with mean age of 63.1 years. All patients were EGFR-mutant BMNSCLC. All patients are Chinese Han ethnicity. Karnofsky performance score consisted of 100 (2 patients), 90 (15 patients), 80 (30 patients), and 70 (8 patients). The histology includes large cell carcinoma (11 patients), squamous cell carcinoma (5 patients), and adenocarcinoma (39 patients). In addition, 35 patients had <3 brain metastases, and 20 patients had >3 brain metastases. Furthermore, 37 patients had history or current smoking experience, and 18 patients never had smoking. Patients were excluded from this study if they had metastases to the other sites of the body, previously treated with EGFR anticancer therapy and WBRT, and patients with severe psychological conditions.

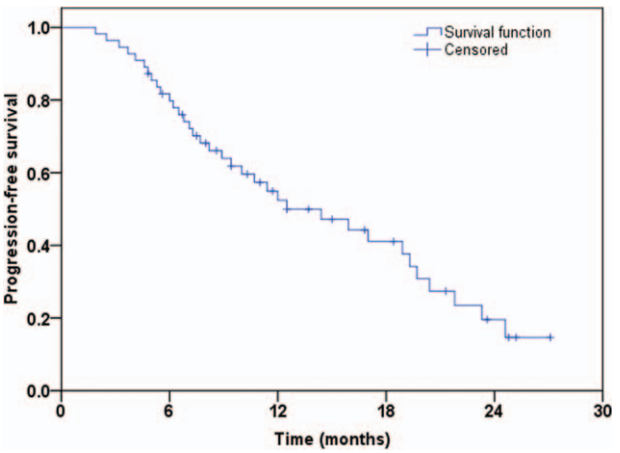

Figure 1. Progression-free survival.

2.3. Intervention

All patients received orally icotinib tablets (125 mg/tablet, 125 mg each time, 3 times daily) until disease progression or adverse events became intolerable. In addition, they concurrently underwent WBRT with 3-Gy fractions once daily, 5 days weekly for a total dose of 30 Gy.

2.4. Outcome measurements

In this study, outcomes included complete response (CR), partial response (PR), stable disease, progress disease (PD), overall response rate (ORR), progression-free survival (PFS), and overall survival (OS). In addition, toxicity was also measured. The tumor size was measured according to the standard of Response Evaluation Criteria in Solid Tumors 1.1. Toxicity was evaluated by using the Common Toxicity Criteria for Adverse Events (V3.0).

2.5. Data analysis

PFS and OS were analyzed by the Kaplan–Meier method. The log-rank test was conducted to perform univariate analysis. All data were analyzed by using Statistical Package for the Social Sciences software (Version 19.0, IBM Corp., Armonk, NY).

3. Results

The CR, PR, CD, PD, and ORR were 38.2%, 52.8%, 5.4%, 3.6%, and 90.1%, respectively (Table 2). The median PFS was 12.5 months (95% confidence interval: 6.8–18.2 months) (Fig. 1), and median OS was 22.3 months (95% confidence interval: 17.2–27.4 months) (Fig. 2).

Table 2

Response rate of all included patients.

Value	CR	PR	SD	PD	ORR
Response rate	21 (38.2)	29 (52.8)	3 (5.4)	2 (3.6)	50 (90.1)

Data are present as number (%).
CR = complete response, ORR = overall response rate, PD = progress disease, PR = partial response, SD = stable disease.

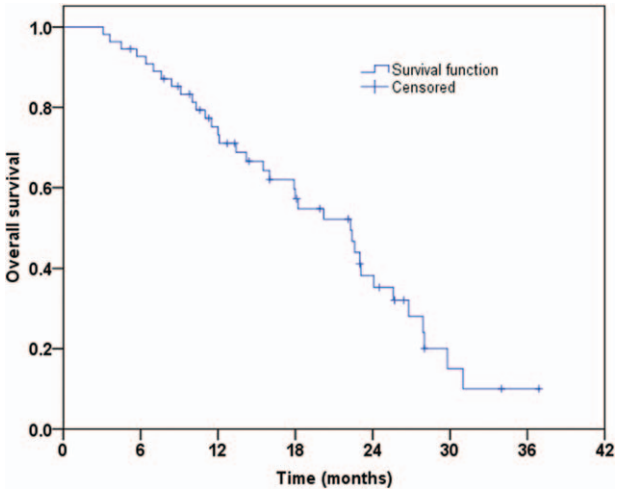

Figure 2. Overall survival.

The toxicity related to the treatments in this study is showed in Table 3. The total toxicity was mild in this study, and all of them occurred in Grades 1 and 2 (Table 3). No grade 3 or higher toxicities were occurred in this study. The most frequencies' toxicities were rash (43.6%) and nausea (41.8%). No death-related treatment medication was recorded in this study.

4. Discussion

Previous studies have investigated the efficacy and safety of IWBRT in patients with BMNSCLC.[13,21–23] One study investigated that whether icotinib is noninferior to gefitinib in patients with NSCLC.[21] Its results showed that icotinib could be used as a new alternative therapy option for pretreated patients with advanced NSCLC.[21] The other study conducted a phase II study to assess the efficacy and safety of IWBRT in Chinese patients with BMNSCLC, and also examined the cerebrospinal fluid (CSF)/plasma concentrations of patients.[22] It found that IWBRT is efficacious and well tolerated in patients with BMNSCLC.[22] Other study explored the dose-escalation toxicity and efficacy of IWBRT on CSF penetration of EGFR-TKIs.[23] The results of this study showed that IWBRT is well tolerated in EGFR-mutated patients with BMNSCLC, and up to the dose of 375 mg tid of icotinib was used.[23] The concentration of CSF seemed to have a potential ceiling effect with the dose escalation.[23] In addition, WBRT did not seem to significantly affect on CSF penetration of icotinib until 4 weeks after the treatment.[23] Another study compared the efficacy of IWBRT with or without chemotherapy in a phase 3 trial in patients with EGFR-mutant BMNSCLC.[13] Its results demonstrated that icotinib was associated with significantly longer intracranial PFS than WBRT combine with chemotherapy.[13] It indicates that icotinib might be used as a better first-line therapeutic option for patients with EGFR-mutant BMNSCLC.[13]

Table 3

Toxicity-related treatment.

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	All grades
Nausea	23 (41.8)	0 (0)	0 (0)	0 (0)	23 (41.8)
Vomiting	5 (9.1)	0 (0)	0 (0)	0 (0)	5 (9.1)
Fatigue	3 (5.5)	0 (0)	0 (0)	0 (0)	3 (5.5)
Headache	16 (29.1)	0 (0)	0 (0)	0 (0)	16 (29.1)
Dizziness	6 (10.9)	0 (0)	0 (0)	0 (0)	6 (10.9)
Constipation	4 (7.2)	0 (0)	0 (0)	0 (0)	4 (7.2)
Diarrhea	6 (10.9)	2 (3.6)	0 (0)	0 (0)	8 (14.5)
Rash	19 (34.5)	5 (9.1)	0 (0)	0 (0)	24 (43.6)
AST/ALT	8 (14.5)	3 (5.5)	0 (0)	0 (0)	11 (20.0)
Dysgeusia	1 (1.8)	0 (0)	0 (0)	0 (0)	1 (1.8)
Bilirubin	2 (3.6)	0 (0)	0 (0)	0 (0)	2 (3.6)

Data are present as number (%).
ALT = alanine aminotransferase, AST = aspartate aminotransferase.

The results of our study are consistent with the previous study.[13] Our study found that the effect of IWBRT in patients with EGFR-mutant BMNSCLC among Chinese Han population is promising with acceptable toxicity. The ORR was 90.1%. In addition, the median PFS and OS were 12.5 and 22.3 months, respectively. The total toxicity was mild without sever adverse events. The most frequencies' toxicities were rash (43.6%) and nausea (41.8%).

There are several limitations in this study. First, this study had a relative small number of patients with EGFR-mutant BMNSCLC, which may be affect the results of this study. Then, this study only focused on the population of Chinese Han ethnicity. Thus, its effect and toxicity of other ethnicities of Chinese population should be investigated in the future. In addition, longer-term effect treatment and assessment should also be considered in the future study.

5. Conclusion

The results of this study demonstrated that IWBRT is effective in patients with EGFR-mutant BMNSCLC among Chinese Han population, and has acceptable toxicity.

Author contributions

Conceptualization: Yu-feng Lv, Ai-ying Jiang, Hai-long Luo, Feng Gao.
Data curation: Ai-ying Jiang, Feng Gao.
Formal analysis: Jing Zhang.
Investigation: Hai-long Luo, Jing Zhang, Feng Gao.
Methodology: Hai-long Luo.
Project administration: Yu-feng Lv.
Resources: Jing Zhang.
Software: Hai-long Luo, Jing Zhang.
Validation: Ai-ying Jiang, Jing Zhang, Feng Gao.
Visualization: Ai-ying Jiang.
Writing – original draft: Yu-feng Lv, Ai-ying Jiang, Hai-long Luo, Jing Zhang, Feng Gao.
Writing – review & editing: Yu-feng Lv, Ai-ying Jiang, Hai-long Luo, Jing Zhang, Feng Gao.

References

[1] Yan X, Chen X, Li G, et al. Two-portal versus three-port video-assist thoracoscopic surgery for early stage nonsmall cell lung cancer: a retrospective study. Medicine (Baltimore) 2017;96:e7796.
[2] Naito Y, Tamiya A, Tamiya M, et al. Efficacy of nanoparticle albumin-bound paclitaxel regimens for relapsed small cell lung cancer: a retrospective analysis. Medicine (Baltimore) 2017;96:e7884.
[3] Jiang X, Hidru TH, Zhang Z, et al. Evidence of elemene injection combined radiotherapy in lung cancer treatment among patients with brain metastases: a systematic review and meta-analysis. Medicine (Baltimore) 2017;96:e6963.

[4] Kazdal D, Harms A, Endris V, et al. Prevalence of somatic mitochondrial mutations and spatial distribution of mitochondria in non-small cell lung cancer. Br J Cancer 2017;117:220–6.
[5] Nicos M, Krawczyk P, Jarosz B, et al. Prevalence of NRAS, PTEN and AKT1 gene mutations in the central nervous system metastases of non-small cell lung cancer. Brain Tumor Pathol 2017;34:36–41.
[6] Mujoomdar A, Austin JH, Malhotra R, et al. Clinical predictors of metastatic disease to the brain from non-small cell lung carcinoma: primary tumor size, cell type, and lymph node metastases. Radiology 2007;242:882–8.
[7] Barnholtz-Sloan JS, Sloan AE, Davis FG, et al. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. J Clin Oncol 2004;22:2865–72.
[8] Yang J, He J, Yu M, et al. The efficacy and safety of platinum plus gemcitabine (PG) chemotherapy with or without molecular targeted agent (MTA) in first-line treatment of non-small cell lung cancer (NSCLC). Medicine (Baltimore) 2016;95:e5599.
[9] Sen F, Tambas M, Ozkaya K, et al. Concomitant etoposide and cisplatin provided improved survival compared with docetaxel and cisplatin in patients with locally advanced non-small cell lung cancer treated with chemoradiotherapy. Medicine (Baltimore) 2016;95:e4280.
[10] Minchom A, Thavasu P, Ahmad Z, et al. A study of PD-L1 expression in KRAS mutant non-small cell lung cancer cell lines exposed to relevant targeted treatments. PLoS ONE 2017;12:e0186106.
[11] Tanaka K, Nosaki K, Otsubo K, et al. Acquisition of the T790 M resistance mutation during afatinib treatment in EGFR tyrosine kinase inhibitor-naïve patients with non-small cell lung cancer harboring EGFR mutations. Oncotarget 2017;8:68123–30.
[12] Hong D, Zhang G, Zhang X, et al. Pulmonary toxicities of gefitinib in patients with advanced non-small-cell lung cancer: a meta-analysis of randomized controlled trials. Medicine (Baltimore) 2016;95:e3008.
[13] Yang JJ, Zhou C, Huang Y, et al. Icotinib versus whole-brain irradiation in patients with EGFR-mutant non-small-cell lung cancer and multiple brain metastases (BRAIN): a multicentre, phase 3, open-label, parallel, randomised controlled trial. Lancet Respir Med 2017;5:707–16.
[14] Loganadane G, Hendriks L, Le Péchoux C, et al. The current role of whole brain radiation therapy in non-small cell lung cancer patients. J Thorac Oncol 2017;12:1467–77.
[15] Wen SW, Han L, Lv HL, et al. A propensity-matched analysis of outcomes of patients with clinical stage I non-small cell lung cancer treated surgically or with stereotactic radiotherapy: a meta-analysis. J Invest Surg 2017;6:1–8.
[16] Iyengar P, Wardak Z, Gerber DE, et al. Consolidative radiotherapy for limited metastatic non-small-cell lung cancer: a phase 2 randomized clinical trial. JAMA Oncol 2017;4:e173501.
[17] Wang P, Zhang D, Guo XG, et al. A propensity-matched analysis of surgery and stereotactic body radiotherapy for early stage non-small cell lung cancer in the elderly. Medicine (Baltimore) 2016;95:e5723.
[18] Tumati V, Iyengar P. SABR rattling with radiation and surgery: paving a path toward refined treatment of early-stage non-small-cell lung cancer. J Oncol Pract 2017;13:77–8.
[19] Zhou L, Lan H, Zhou Q, et al. Plasma angiopoietin-2 is persistently elevated after non-small cell lung cancer surgery and stimulates angiogenesis in vitro. Medicine (Baltimore) 2016;95:e4493.
[20] Shen H, Cao Y, Li X, et al. Surgical intervention improves survival for metastatic non-small cell lung cancer patients. Medicine (Baltimore) 2016;95:e3800.
[21] Shi Y, Zhang L, Liu X, et al. Icotinib versus gefitinib in previously treated advanced non-small-cell lung cancer (ICOGEN): a randomised, double-blind phase 3 non-inferiority trial. Lancet Oncol 2013;14:953–61.
[22] Fan Y, Huang Z, Fang L, et al. A phase II study of icotinib and whole-brain radiotherapy in Chinese patients with brain metastases from non-small cell lung cancer. Cancer Chemother Pharmacol 2015;76:517–23.
[23] Zhou L, He J, Xiong W, et al. Impact of whole brain radiation therapy on CSF penetration ability of icotinib in EGFR-mutated non-small cell lung cancer patients with brain metastases: results of phase I dose-escalation study. Lung Cancer 2016;96:93–100.