Chinese-German J Clin Oncol
DOI 10.1007/s10330-014-1308-1
June 2014, Vol. 13, No. 6, P259–P263

Prognostic factors to predict survival in non-small-cell lung cancer with brain metastasis

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Received: 21 March 2014 / Revised: 15 April 2014 / Accepted: 5 May 2014

Abstract ***Objective:*** The purpose of the study was to assess prognostic factors to predict overall survival (OS) and progression-free survival (PFS) in non-small-cell lung cancer (NSCLC) with brain metastasis (BM). ***Methods:*** From November 2011 to March 2013, the clinical data of 31 NSCLC cases with BM treated with multiple modalities including brain radiotherapy alone, systemic chemotherapy, whole brain radiotherapy (WBRT) combined with tyrosine kinase inhibitor (TKIs). The efficacy and adverse reaction were evaluated after treatment. ***Results:*** In terms of intracranial lesions, the objective response rate (ORR) and the disease control rate (DCR) were 22.6% and 90.3%, respectively. As for systemic disease, ORR and DCR were 32.3% and 93.5%, respectively. The median time to progression-free survival (PFS) was 298 days (95% CI: 258.624–337.376 days), whereas in the epidermal growth factor receptor (EGFR) mutation patients was 331 days. Patients who received EGFR-TKIs combined with brain radiation had better response rate (RR) than those only brain radiation. Univariate analysis showed that the EGFR-mutations could predictive factors for PFS, and not to other clinical pathological features. The most common toxicities were rash and diarrhea, but all were well-tolerated. ***Conclusion:*** EGFR-mutations is the independent prognostic factors affecting the survival rates of NSCLC patients with BM. Through the clinical observation, icotinib combined with WBRT may be effective on brain metastases in NSCLC patients, and toxicities are tolerable, which worth further study.

Key words non-small-cell lung cancer (NSCLC); brain metastases (BM); epidermal growth factor receptor (EGFR) mutation; prognosis

Non-small-cell lung cancer (NSCLC) is the leading cause of cancer-related death worldwide [1]. Of the patients who are diagnosed with solitary brain metastases, 30% to 70% are confirmed to have lung cancer as the primary lesion [2]. Approximately 40% of all patients with lung cancer suffer from brain metastases in the course of their disease [3]. The standard treatment for these patients consists of a short course of palliative whole brain radiotherapy (WBRT). Although patients with brain metastases are generally treated with corticosteroids and WBRT, the prognosis of patients with brain metastases is still disappointing. WBRT extends survival by only 14 to 21 weeks, even when it achieves palliative improvement in neurological symptoms [4]; refractory brain metastases cause death in 25% to 50% of these patients [5]. Although gamma knife surgery results in tumor reduction, stabilization, or disappearance in approximately 90% of the patients, the survival rate appears to be similar to that with WBRT [6]. Systemic platinum-based chemotherapy has also been shown to contribute to comparable response rates (RRs) for brain metastases from lung cancer and may be an option for management of brain metastases. However, the superiority of chemotherapy to radiotherapy remains unclear.

The epidermal growth factor receptor (EGFR), a transmembrane tyrosine kinase protein, is common in NSCLC, and its presence is associated with a poor prognosis. Icotinib is a tyrosine kinase inhibitor specific for epidermal growth factor receptor (EGFR), which can be administered orally and has already been approved in China for NSCLC.

Overexpression of EGFR in tumors is associated with reduced local control after radiation therapy (RT) [8]. Preclinical data have shown that inhibition of EGFR increases local tumor control after RT, and a prospective Phase III trial of patients with head-and-neck tumors found combined RT with the anti-EGFR antibody cetuximab to increase both local tumor control and survival [9–10]. Because of the RRs reported with EGFR inhibitors for brain metastases from NSCLC and the radiation-enhancement effect of EGFR inhibition, we hypothesized that combining icotinib with WBRT might improve the dismal prognosis

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Table 1 Patients demographics and disease characteristics

Characteristics	*n*	%
Gender		
Male	15	48.4
Female	16	51.6
Age (years)		
> 65	14	45.2
≥ 65	17	54.8
Tumor histologic Type		
Adenocarcinoma	24	77.4
Others	7	22.6
WHO PS		
1	18	58.1
2	13	41.9
Icotinib treatment		
Yes	23	74.2
No	8	25.8
Brain metastases		
1	9	29.0
> 1	22	71.0
EGFR mutant		
Yes	19	61.3
No	4	12.9
Unknown	8	25.8
WBRT		
Yes	25	74.2
No	6	25.8

WHO: World Health Organization; PS: performance status

of these patients. Therefore, we performed a prospective study to assess the safety and tolerability of this combination.

Materials and methods

Patients selection

There were 31 patients in this study patients with histologic or cytologic confirmation of NSCLC with were brain metastases assessed for eligibility. The 31 evaluable patients consisted of 17 women and 14 men, with a median age of 63 years (range, 47–72 years). Patient demographics and disease characteristics for enrolled patients (n = 31; Table 1).

Procedures

Icotinib was given orally in as dose of 125mg 8-hourly. Whole brain RT was delivered to a total dose of 30 Gy in 10 once-daily fractions, and the overall treatment time was 2 weeks. Patients were placed in the supine position with customized immobilization masks. The treatment was delivered to the brain using lateral-opposing portals with 6-MV photons. Steroids were administered at the discretion of the treating physician, as indicated by the clinical signs and symptoms. Dose-limiting toxicity was defined as Grade 4 skin toxicity, Grade 3 or 4 diarrhea not improving with the addition of loperamide at a maximal dose during 48 h, any other Grade 3 or 4 clinically significant, non-hematologic toxicity (excluding Grade 3 nausea and any grade of alopecia), and any toxicity that resulted in a delay in treatment and a dose reduction. The maximal tolerated dose was defined as the dose of icotinib that could be safely administered with WBRT that resulted in tolerable, manageable, and reversible toxicity.

Endpoints and statistical analysis

The baseline assessments included medical history, physical examination, neurologic examination, routine laboratory tests, CT scans of the chest and abdomen, and CT or MRI scans of the brain. Patients were assessed for toxicity and clinical response by the radiation oncologist and/or pulmonologist at weeks 1 and 2 of WBRT and at 2 weeks, 4 weeks, and 2 months and then every 2 months thereafter until disease progression and/or death. MRI scans of the brain and CT scans of the chest were performed at 3-month intervals.

The response was evaluated based on the response evaluation criteria in solid tumors criteria [11], which was divided into complete response, partial response，stability of disease and progress of disease. Complete response (CR) + partial response (PR) stands for valid (RR), CR + PR + stability of disease (SD) stands for disease control (disease control rate, DCR). We assessed quality of life with the use of the fourth edition of the Functional Assessment of Cancer Therapy–Lung (FACT-L) questionnaire and the Lung Cancer Symptoms Scale [12]. Toxic effects were monitored and graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events version 3.0 [13]. To analyse progression-free survival (PFS), survival curves were drawn using the Kaplan-Meier method. Survival differences were evaluated using the log-rank test. Clinical data were analysed using the Pearson's chi-square test. All analyses were performed using SPSS statistical software (SPSS Version 19.0 for Windows, SPSS Inc, USA).

Results

Curative effect and related factors

In terms of intracranial lesions, according to the criterion of curative effect of solid tumor follow- up PR 7 patients, SD 21 patients and progress of disease (PD) 3 patients. The objective RR and the disease control rate (DCR) were 22.6% and 90.3%, respectively. In terms of intracranial lesions, according to the criterion of curative effect of solid tumor follow- up PR 10 patients, SD 19 patients and PD 2 patients. The objective RR and the DCR were 32.3% and 93.5%. There is not significant correlation to the efficacy among tumor pathological type,

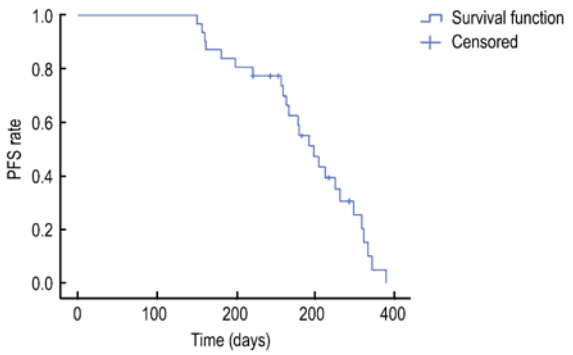

Fig. 1 The whole group PFS data analysis

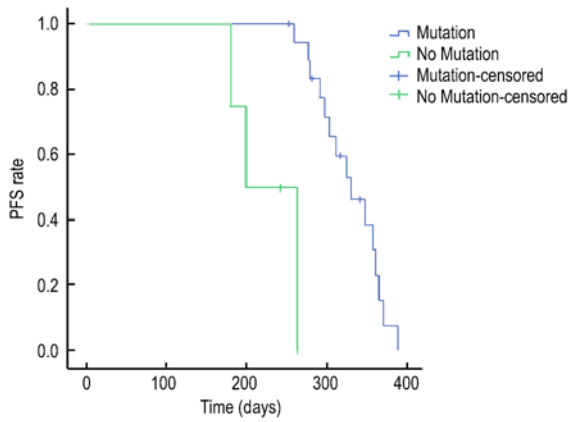

Fig. 2 The median PFS between EGFR-mutant tumors and wild-type tumors

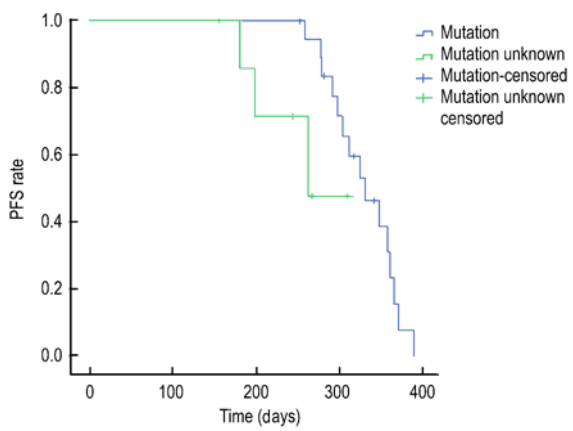

Fig. 3 The median PFS between EGFR-mutant tumors and unknown-type tumors

sex, age, the number of brain metastases and radiation to the brain ($P > 0.05$). And the results indicated that EGFR mutation status and icotinib combined with WBRT had evident positive correlation with the efficacy.

Subgroup analysis: 6 cases with intracranial lesions without radiotherapy were evaluated for SD. There was 18 cases oral icotinib 1 months after radiotherapy, intracranial lesions evaluation showed that 5 cases obtained PR, 9 of them pharmacological remission SD, 4 of them PD. 7 cases were treated with icotinib combined with radiotherapy, intracranial lesions evaluation showed that 3 patients achieved PR, 3 patients achieved SD and 1 patients achieved PD. Icotinib combined with radiation better than radiation single in objective RR (ORR), the difference was not statistically significant.

PFS effect and related factors

Current data (as of March 1, 2013) of the 31 patients considered adhere to this established trend. Of these cases, 17 patients had disease progression. In the full analysis set, median PFS was 298 days (95% CI: 258.624–337.376 days; Fig. 1). PFS has nothing to do with tumor pathological type, sex, age, PS score, the number of brain metastases and radiation to the brain, but the efficacy has relation with EGFR mutation status (Table 2). In this study, the overall median PFS was 331 days (95%CI: 289.314–372.686 days) with EGFR-mutant tumors and 199 days (95% CI: 145.427–252.573 days) with wild-type tumors, the difference was statistically significant ($P = 0.002$; Fig. 2). PFS was 331 days (95%CI: 289.314–372.686 days) with EGFR-mutant tumors and 214 days (95%CI: 175.307–282.132 days) with wild-type tumors, the difference was statistically significant ($P = 0.004$; Fig. 3).

Toxicity

Toxicity was generally Grade 1 or 2, with the most frequent toxicities being fatigue, acneiform rash, anorexia, diarrhea, nausea. No Grade 3 or greater toxicity was observed. The side effect palliation moves soon, did not need the special processing (Table 3).

Discussion

Of patients with NSCLC, a large part present with metastatic disease will have poor prognosis. Small retrospective clinical studies showed that under gefitinib and erlotinib treatment of brain metastases from NSCLC have a certain effect [14–15], most reports is carried out mainly on retrospective observation with small sample sizes, RR range was 10%–10%, DCR in 27%–100% [16–22]. According to ICOGEN trial statistics data show that a greater proportion of objective responses in patients with mutated EGFR than in those with wild-type EGFR. Our study shows that in terms of intracranial lesions, the ORR and the DCR were 22.6% and 90.3%. The ORR and the DCR of systemic disease were 32.3% and 93.5%, respectively. Zeng *et al* found that gefitinib combined with radiation better than gefitinib single in DCR, it is possible that radiation can disrupt the blood-brain barrier, which could enable more successful delivery of targeted drugs, raise

Table 2 The prognosis of 31 NSCLC patients with brain metastases

Characteristics	*n*	Median PFS (95% CI)	*P*
Gender			
Male	15	6.2 (4.8–8.8)	0.861
Female	16	7.3 (5.1–9.5)	
Age (years)			
> 65	14	7.5 (4.8–9.3)	0.692
≥ 65	17	6.2 (3.5–7.8)	
Tumor histologic Type			
Adenocarcinoma	24	6.5 (4.1–8.6)	0.312
Others	7	6.1 (5.1–7.8)	
WHO PS			
1	18	9.8 (4.6–15.3)	0.304
2	13	4.2 (3.1–7.5)	
Icotinib treatment			
Yes	23	6.5 (5.1–8.7)	0.876
No	8	6.3 (3.6–7.2)	
Brain metastases			
1	9	6.8 (5.1–9.8)	0.326
> 1	22	6.0 (4.5–8.0)	
EGFR mutant			
Mutation	19	10.2 (3.6–17.3)	0.002
No mutation	4	4.7 (3.1–6.5)	
WBRT			
Yes	20	7.4 (5.1–10.2)	0.343
No	11	6.0 (4.5–8.8)	

Table 3 Adverse reaction of icotinib in NSCLC brain metastasis

Adverse events	Toxicity classification			
	I	II	III	IV
Fatigue	9	2	0	0
Acneiform rash	6	2	1	0
Anorexia	8	1	0	0
Diarrhea	3	1	0	0
Nausea	4	0	0	0
Leucopenia	2	1	0	0
Hypohepatia	1	0	0	0

therapeutic effect and improve life quality [23]. Through this study, prior radiation and icotinib concurrent with radiotherapy have a better ORR than icotinib monotherapy, however, there were no statistically significant and PFS difference, this perhaps was small related with this research sample choice.

Several studies have shown that positive EGFR mutations are associated with better survival and a better clinical response with EGFR-TKIs than are wild-type-mutations [24–26]. Gow *et al* and Shimato *et al* found that patients with EGFR mutations seem to have longer PFS [27–29]. From this study we found that EGFR mutations can influence PFS. EGFR mutations have longer PFS than in those with wild-type EGFR (331 days vs 199 days, $P = 0.002$). Clinically, the results suggest that the patients will benefit from EGFR mutations. Moreover the PFS showed increasing direction following experimental days.

The combination was well tolerated, with no deterioration in neurologic symptoms, and all patients were able to complete the 2 weeks of WBRT. Treatment-related toxicity was mainly limited to Grade 1 or 2 and was consistent with the previously documented toxicity profile of icotinib [30]. The most common treatment-related toxicities were fatigue, acneiform rash, anorexia, diarrhea, taste alteration, weight loss, nausea, and dyspnea.

In this study, we focused on objective response to brain metastases, but survival benefit could not be evaluated from our data. We recently reported that EGFR mutations were not only a good predictor of tumor response but also factors that prolonged the survival period for the patients with recurrent NSCLC treated with icotinib. Further prospective trials should also determine the association between EGFR gene status and survival benefit to brain metastases from NSCLC.

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