

RESEARCH ARTICLE

Clinical Observation of Whole Brain Radiotherapy Concomitant with Targeted Therapy for Brain Metastasis in Non-small Cell Lung Cancer Patients with Chemotherapy Failure

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Abstract

Objective: To investigate the clinical effects of whole brain radiotherapy concomitant with targeted therapy for brain metastasis in non-small cell lung cancer (NSCLC) patients with chemotherapy failure. **Materials and Methods:** Of the 157 NSCLC patients with chemotherapy failure followed by brain metastasis admitted in our hospital from January 2009 to August 2012, the combination group (65 cases) were treated with EGFR-TKI combined with whole brain radiotherapy while the radiotherapy group (92 cases) were given whole brain radiotherapy only. Short-term effects were evaluated based on the increased MRI in brain 1 month after whole brain radiotherapy. Intracranial hypertension responses, hematological toxicity reactions and clinical effects of both groups were observed. **Results:** There were more adverse reactions in the combination group than in radiotherapy group, but no significant differences were observed between the two groups in response rate (RR) and disease control rate (DCR) ($P>0.05$). Medium progression free survival (PFS), medium overall survival (OS) and 1-year survival rate in combination group were 6.0 months, 10.6 months and 42.3%, while in the radiotherapy group they were 3.4 months, 7.7 months and 28.0%, respectively, which indicated that there were significant differences in PFS and OS between the two groups ($P<0.05$). Additionally, RPA grading of each factor in the combination group was a risk factor closely related with survival, with medium PFS in EGFR and KRAS mutation patients being 8.2 months and 11.2 months, and OS being 3.6 months and 6.3 months, respectively. **Conclusions:** Whole brain radiotherapy concomitant with target therapy is favorable for adverse reaction tolerance and clinical effects, being superior in treating brain metastasis in NSCLC patients with chemotherapy failure and thus deserves to be widely applied in the clinic.

Keywords: Non-small cell lung cancer - brain metastasis - whole brain radiotherapy - targeted therapy - clinical effect

Asian Pac J Cancer Prev, **14** (10), 5699-5703

Introduction

Brain metastasis in non-small cell lung cancer (NSCLC) is the most common intracranial metastatic tumors, and 10% NSCLC patients are diagnosed with brain metastasis initially while 30%~50% in certain stage. NSCLC in progressive stage has great rate of developing brain metastasis and poor prognosis (Li et al, 2013; Liu et al., 2013; Natukula et al., 2013). Medium survival time (MST) without any treatment is only 1 month in NSCLC patients with brain metastasis, while it is 2~3 months in those being positively treated with dehydration and hormone, and 6 months after whole brain radiotherapy (Gianfranco et al., 2012). With the development of video techniques, some minimal metastasis can be observed at early stage, and single or limited brain metastasis can be treated by neurosurgery or cranio-cerebral stereotactic radiotherapy, but most patients are free with local therapeutic indications due to multiple intracranial

metastasis.

Most chemotherapeutic drugs are poor in treating brain metastasis except brain radiotherapy. Though blood brain barrier (BBB) around brain metastasis is damaged, the concentration of chemotherapeutic drugs is still low, which is possibly associated with the pump-out of chemotherapeutic drugs by tumor cells from efflux pump. Semustine and temozolomide, etc., which have higher rate of passing through BBB, are effective in primary malignant tumors of central nervous system, such as glioma, but are poor in treating brain metastasis in NSCLC.

As a micro-molecule compound, epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) can pass through BBB in certain proportion, becoming an important theoretical basis for the treatment of brain metastasis in NSCLC. As the studies move along, signal path of EGFR is found to be closely connected with radioactive antagonism of tumor cells whose

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Table 1. General Data

Characteristics	Cases
Age	
>70 years	37
≤70 years	120
Gender	
Male	103
Female	54
ECOG score	
0	3
1	93
2	61
Smoking history	
>300/year	73
≤300/year	84
Primary tumor sites	
Upper lobe	48
Middle and lower lobes	109
Pathological patterns	
Squamous carcinoma	43
Adenocarcinoma	79
Adeno-squamous carcinoma	15
Large cell carcinoma	12
Unclassified	8

radioactive sensibility can be strengthened by EGFR inhibitor, whereas EGFR-TKI was found to be capable in strengthening the radioactive sensibility through multiple approaches (Miyata et al., 2006; Colquhoun et al., 2007). Though EGFR-TKI is widely appreciated in second-line treatment of NSCLC, the effect and influencing factors of whole brain radiotherapy concomitant with TKI on brain metastasis need to be further studied and summarized. However, certain experiences were still obtained in this study by observing the combined treatment on NSCLC.

Materials and Methods

General data

A total of 157 NSCLC patients with brain metastasis after chemotherapy failure admitted in Shanghai Pulmonary Hospital from January, 2009 to August, 2012 were selected as study objects. Inclusion criteria: (1) All patients had definite pathological patterns and should have obtained pathological samples from Shanghai Pulmonary Hospital, including surgical pathological tissues or sections, pneumocentesis or biopsy samples, liquid-based cytology test, lymph node or other metastasis puncture or biopsy samples, fiberoptic bronchoscopy biopsy, brush biopsy, or lavage fluid-based cytology test, etc.; (2) All patients were diagnosed with NSCLC with pathological patterns being squamous carcinoma, adenocarcinoma, adeno-squamous carcinoma, large cell carcinoma and unclassified ones; (3) All patients were observed with brain metastasis after first- or second-line chemotherapy failure, and with no history of whole brain radiotherapy or EGFR-TKI therapy before this study. (4) Single whole brain radiotherapy or the one combined with EGFR-TKI therapy was performed.

According to inclusion criteria, 157 patients were selected with 103 males and 54 females, aging from 35 to 81 years (medium age: 66), as shown in Table 1.

Table 2. Results of Gene Detection

Gene detection	Cases
EGFRmutation	43
KRAS mutation	16
Simultaneous mutations	1
Double negative	97

EGFR and KRAS mutation detections

EGFR and KRAS mutation detections were conducted using 21 and 7 mutation detection kits of ADx-ARMSEGFR gene brought from Xiamen ED biopharmaceutical co., LTD. Of all patients, in those with adenocarcinoma, 47.3% were EGFR mutation with total rate being 27.4% (43/157) while KRAS mutation accounted for 10.2% (16/157), and only 1 simultaneous mutation of EGFR and KRAS was observed (Table 2).

EGFR-TKI and whole brain radiotherapy

Single whole brain radiotherapy or the one combined with EGFR-TKI therapy was performed to patients with brain metastasis after radiotherapy failure. Of all patients, combination group (65 cases) was treated EGFR-TKI concomitant with whole brain radiotherapy while radiotherapy group (92 cases) was given single whole brain radiotherapy.

EGFR-TKI therapy: 250 mg/d Gefinitib or 150 mg/d Erlotinib, and the drug-withdrawal principles included disease progression, death or poor tolerance of drugs. In combination group, 43 patients were treated with Erlotinib and 22 with Gefinitib.

Whole brain radiotherapy: Spiral CT scan was applied first with the range from vertex to skull base and the thickness of 0.5 cm, which was then transferred to TPS plan system by network. Drawing the outline of targeted area: Targeted areas included whole brain volume, and were outlined with extension of 0.5~1.5 cm based on PTV according to individual symptoms and setup errors, and basic structures of organs were also outlined, including eyeballs, optic nerves, optic chiasma and brainstem. Hypo-fractionated conformal radiotherapy was performed to all patients, and the total volume of 90% PTV was 29.37~41.24 Gy, 3 Gy/d, 5 times/week.

Efficacy evaluation

Efficacy evaluation criteria: Short-term effect was evaluated according to the increased MRI in brain 1 month after whole brain radiotherapy. Effect: complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Total response rate (RR) = CR+PR/total cases, DCR=CR+PR+SD/total cases. Long-term effect: progression free survival (PFS), medium survival time (OS), 1- and 2-year survival rates.

Adverse reaction evaluation

Drug and radiotherapy reactions were classified according to WHO anti-cancer drugs adverse reaction criteria and RTOG radioactive injury classification criteria made by American Radiation Therapy Oncology Group for tumors, respectively.

Table 3. General Data Comparison of Two Groups

Groups	Combination group (n=65)	Radiotherapy group (n=92)	X ²	P
Age			0.068	0.795
>70 years	16	21		
≤70 years	49	71		
Gender			0.813	0.367
Male	40	63		
Female	25	29		
ECOG			0.096	0.953
0	1	2		
1	39	54		
2	25	36		
Smoking history			0.521	0.470
>300/year	28	45		
≤300/year	37	47		
Primary tumor site			0.434	0.510
Upper lobe	18	30		
Middle and lower lobes	47	62		
Pathological patterns			1.796	0.773
Squamous carcinoma	16	27		
Adeno-carcinoma	33	46		
Adeno-squamous carcinoma	6	9		
Large cell carcinoma	5	7		
Unclassified	5	3		

Table 4. Intracranial Hypertension Responses and Hematological Toxicity Reactions [n(%)]

AR	Combination group (n=65)	Radiotherapy group (n=92)	X ²	P
Headache	23(35.4%)	28(30.4%)	0.426	0.514
Nausea and vomiting	27(41.5%)	37(40.2%)	0.028	0.868
Dizziness	15(23.1%)	20(21.7%)	0.039	0.843
Granulocytopenia	7(10.8%)	8(8.7%)	0.190	0.663
Reduced hemoglobin	9(13.8%)	10(10.9%)	0.317	0.573

Statistical data analysis

SPSS13.0 software was adopted for statistical analysis, Chi-square test and Cox regression model were used for one-way analysis and multi-variate analysis of survival respectively, while survival rate was calculated by Kaplan-Meier and detected using Logrank method. The significant level was set as $P < 0.05$.

Results

General data

Table 3 shows no statistical differences in clinical data of two groups.

Adverse reactions (AR)

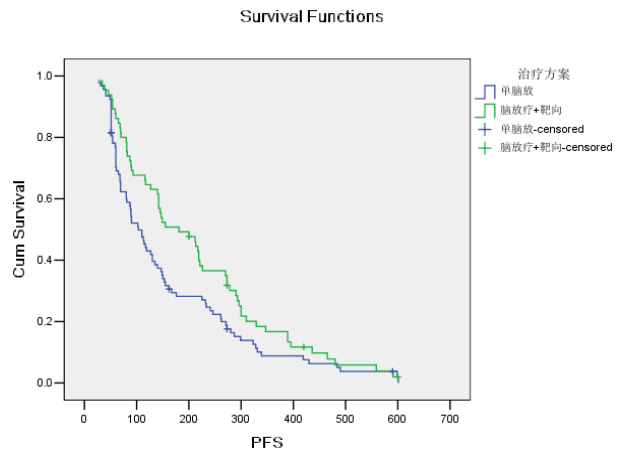
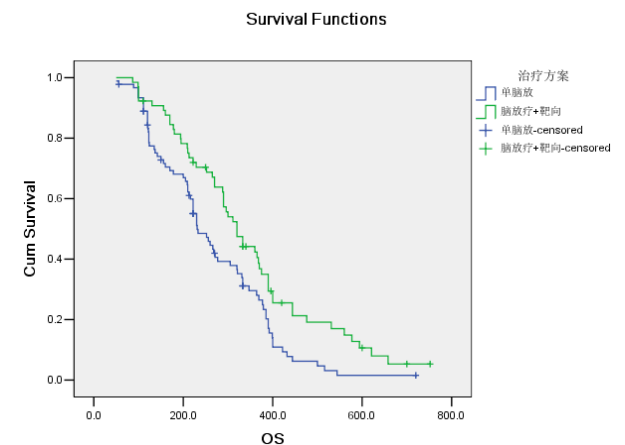
The terminal follow-up was ended on August 30th, 2012. The average dosage given on eyeballs, optic nerves, optic chiasma and brainstem, etc., were equal to those performed on normal tissues in both groups, and Table 4 is showing the detailed intracranial hypertension responses and hematological toxicity reactions. Additionally, other adverse reactions were also observed in combination group, including 41 rash (47.7%), 5 interstitial pneumonia (7.7%) and 5 diarrhea (7.7%).

Clinical effect

In combination group, there were 5 CR, 45 PR, 13

Table 5. Combined Effect of Different Targeted Drugs

Programs	Erlotinib	Gefitinib	X ²	P
RR/%	79.1	72.7	0.330	0.566
DCR/%	97.7	95.5	0.240	0.624
Medium PFS/month	6.9	5.5	0.530	0.468
Medium OS/month	11.2	9.1	1.060	0.303

**Figure 1. PFS Survival Curve of Two Groups****Figure 2. OS Survival Curve of Two Groups**

SD and 2 PD with RR and DCR being 76.9% and 96.9% respectively, while in radiotherapy group there were 7 CR, 58 PR, 17 SD and 10 PD with RR and DCR being 70.7% and 89.1% respectively, which showed no differences in RR and DCR ($P > 0.05$). Medium PFS, medium OS and 1-year survival rate in combination group were 6.0 months, 10.6 months and 42.3% respectively, while in radiotherapy group were 3.4 months, 7.7 months and 28.0%, which showed significant differences in PFS and OS ($P < 0.05$), as shown in Figures 1 and 2. Additionally, RPA grade of each factor in combination group was risk factor that closely related with survival, with medium PFS and OS in EGFR and KRAS mutations patients being 8.2 months and 3.6 months, and OS being 11.2 months and 6.3 months, respectively.

Combined effect of different targeted drugs

As shown in Table 5, there were no significant differences in short-term effect and survival rate between two groups, however, Erlotinib was slightly higher in medium PFS and OS than Gefitinib.

Discussion

In EGFR-TKI, Erlotinib is always considered to have the highest pass rate through BBB, and is commonly used on clinical brain metastasis (Morris et al., 2013). Clinical research found that BBB pass rate of Erlotinib = cerebral spinal fluid concentration (Ccsf)/plasma concentration, which was about 7% while that of active metabolite of Erlotinib (OSI-420) was about 9%. The concentration of Erlotinib in intracranial metastasis was obviously concentrated, which was evidently higher than in normal brain parenchyma (Harth et al., 2013; Shaw et al., 2013). And Erlotinib marked by isotope C11 was selected as PET-CT tracer, being capable in revealing its distribution in brains of NSCLC patients.

Higher BBB pass rate and targeted accumulation of intracranial metastasis are two important properties of Erlotinib in NSCLC, therefore, the combined function of treating brain metastasis and strengthening radio-sensitivity of Erlotinib is the theoretical basis of EGFR-TKI concomitant with whole brain radiotherapy (Windsor et al., 2013). Zhang et al., explored the clinical effect and tolerance of 150 mg/d Erlotinib concomitant with 40Gy/20Fx whole brain radiotherapy for 12 NSCLC patients with multiple brain metastasis, indicating some satisfied achievements that total RR, CR, PR, medium PFS, medium OS were 100%, 66.7%, 33.3%, 8 months and 10 months respectively, with 3 rash in I stage and 1 mild diarrhea (Zhang et al., 2007).

In this study, follow-up was performed on 157 NSCLC patients and the amount of patients with brain metastasis in initial diagnosis and underwent first-line EGFR-TKI therapy was too small to be enrolled. Statistics of general data of NSCLC patients with brain metastasis after first- or second-line chemotherapy failure demonstrated that the rate of males was higher than that of females by 31.2%, and more than 39% patients with 2 scores of ECOG PS score received whole brain radiotherapy, suggesting that PS score would decrease and the total score of brain metastasis was lower in patients with intracranial metastasis after chemotherapy failure than in patients with metastasis on other sites. Of all cases, the ratio of adenocarcinoma was evidently higher than other patterns, which was consistent with the total development trend of lung cancer (Chamberlain 2013; Hassler et al., 2013).

In this study of advanced brain metastasis, 65 patients received EGFR-TKI concomitant with whole brain radiotherapy while other 92 were treated with whole brain radiotherapy only, and less than 10% patients were given EGFR gene detection before treatment. According to central detection of pathological samples collected by Pathology Department, EGFR mutation rate of adenocarcinoma was 47.3% and total EGFR mutation rate was 27.4%, being apparent higher than other patterns of NSCLC. Meanwhile, EGFR and KRAS mutation rates were 77.1% and 10.2% respectively in non-smoking females with adeno-carcinoma, and KRAS mutation rate was 17.8% in patients with cigarettes >300/year, demonstrating that KRAS mutation was in certain association with smoking. Only 1 patient was observed with simultaneous EGFR and KRAS mutations, which showed that EGFR

and KRAS genes were in mutual exclusion.

In this retrospective study, chemotherapeutic drugs could not enter BBB, which had limited effect on remedy of brain, so the first- or second-line treatment was not introduced in detail. There were no significant differences between two groups in age, gender, ECOG score, pathological patterns, as well as EGFR and KRAS mutations. EGFR-TKI was performed to combination group, in which Erlotinib and Gefitinib were given to 43 and 22 patients respectively, and there was no specificity in selecting targeted drugs. Similarly, patients without Icotinib were also selected. And we also gave great attention to the results of a phase III clinical study of Icotinib combined with whole brain radiotherapy conducted by Shanghai Pulmonary Hospital presently.

In this study, all patients were given EGFR-TKI concomitant with whole brain radiotherapy, while CT analog scanning, targeted areas outlining, TPS plan as well as radiotherapy setup were administrated with dosage of whole brain radiotherapy being about 30Gy/10Fx. After treatment, hematological toxicities and intracranial hypertension symptoms were found to be similar in two groups, whereas the interstitial pneumonia was 7.7% in combination group, and there was no statistical difference in adverse reactions. RR and DCR were higher in combination group than in radiotherapy group (76.9% vs 70.7%, 96.9% vs 89.1%), but no significant differences were obtained, indicating that whole brain radiotherapy was superior in local treatment. So far, whole brain radiotherapy is still the most effective and irreplaceable therapy in local treatment of brain metastasis (Truc et al., 2013). However, the promotion of local effect in radiotherapy was not obvious when combined with EGFR-TKI, suggesting that there was great difference in short-term effect between brain radiotherapy and EGFR-TKI which was limited in local effect (Dziggel et al., 2013).

PFS and OS in combination group were 6.0 and 10.6 months, higher than radiotherapy group by 2.6 and 2.9 months, respectively, and the differences were statistically significant ($P < 0.05$). Moreover, whole PFS and OS were evidently increased when combined with EGFR-TKI therapy, which brought about inspiring achievements. J. Welsh et al, reported a phase II clinical study of Erlotinib concomitant with whole brain radiotherapy on 40 NSCLC patients with brain metastasis until disease progression or death, in which 50% patients were treated with 30 Gy/10Fx radiotherapy and the others with 35 Gy/14 Fx while 18 patients received EGFR mutation detection. After 21 months of follow-up, MST was observed to be 10.9 months, demonstrating that rash was correlated with survival, while 6 and 2 patients were with dermal toxicity and diarrhea in grade III, respectively (J. Welsh et al., 2011). Shenglin Ma et al, studied the clinical effect of oral Gefitinib concomitant with whole brain radiotherapy (40Gy/20Fx) on 21 NSCLC patients with brain metastasis admitted from October, 2005 to January, 2007, and the results showed that RR, DCR, medium PFS and medium OS were 81%, 95%, 10 months and 13 months, while the rates of rash, diarrhea and diarrheas in grade III were 86%, 43% and 15%, respectively, revealing that Gefitinib concomitant with whole brain radiotherapy were favorable

in drug-tolerance and preliminary effect (Shenglin et al., 2009).

In combination group, only RPA was in association with survival, and no significant connections were recorded between survival and the EGFR and KRAS mutations. Medium PFS and OS in patients with EGFR mutation were 8.2 months and 11.2 months respectively, slightly higher than those of whole patients, whereas they were 4.6 months and 9.3 months in patients with KRAS mutation respectively, lower than those of whole patients, indicating that KRAS mutation could induce drug-tolerance of EGFR-TKI and antagonistic factor of radiotherapy. Additionally, the less mutation cases or the heterogeneity of gene mutations in primary tumor and metastasis of lung cancer might be the reason why EGFR and KRAS mutations were not related with survival (Lao et al., 2013).

In summary, RR and DCR of Gefitinib and Erlotinib in combination group were comparative, but they were superior in patients received Gefitinib. Though there was no statistically significant difference, Erlotinib showed certain advantages and higher pass rate of BBB in treating brain metastasis (Brown et al., 2013).

Acknowledgements

Appreciation is extended to the contributions from Pathological Department of Shanghai Pulmonary Hospital and to the guidance of statistical analysis from Statistical Teaching and Research Office in The Second Military Medical University.

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